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ENOS NEWS

The Newsletter for the Efficacy in Nitric Oxide Stroke Trial

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ENOS: The Future

I am delighted to tell you that ENOS has received a 2 year funding of extension from the Medical Research Council. As you know, we were aiming to recruit 5,000 patients by September 2011. It became clear some time ago that we would not reach this figure and in this time frame would need to consider what to do.

It has also become clear that dichotomous analyses (based on comparing the rates of poor outcomes - death or dependency - between the treatment groups) is inefficient statistically and that analyses comparing the distribution of Rankin Scores (so called shift analysis) is more powerful. The result of this is that the sample size can be reduced to 3,500+ whilst retaining the same statistical power. We have amended the Statistical Analysis Plan to reflect this change - this is published on the documents page of the ENOS website.

Taking these two pieces of information together, the ENOS Trial Steering Committee (TSC) decided to approach MRC for a two year extension with the aim of recruiting at least 3,500 patients by September 2013. I am pleased to say that MRC have supported this request. Following the annual TSC meeting in January I wanted to share this good news with you.

To reach 3,500 patients we need a recruitment rate of at least 45 patients per month. ENOS achieved this in late 2009 and January (48) so please keep recruiting. Looking through the activity of ENOS sites it is evident that there are:
1. A number of stalwarts who recruit regularly, often more than once a month (so it can be done). If you are one of these, please keep going.
2. Some sites who recruit infrequently, say once a quarter. Please try to enrol patients more often.
3. A number of sites who, surprisingly, have had their start-up visit but never recruited any patients. Bearing in mind the hard 'bureaucratic' work required to reach start-up, please do join the more interesting part of the trial, namely recruitment!

The world of acute BP-stroke trials is evolving and ENOS has become even more relevant now that two other important trials have or will shut down early:
1. The COSSACS trial was testing the question of continuing versus stopping pre-stroke antihypertensive medication in patients with ischaemic or haemorrhagic stroke. It stopped, for lack of funding, after recruiting 761 patients although the aim was to recruit several thousand patients. As a result, it is unlikely that COSSACS will provide definitive information on the management of pre-stroke antihypertensive medication. The results for COSSACS will be presented this May at the European Stroke Conference (Barcelona). We will update Investigators with the results of COSSACS once we know them, and whether they have any implications for ENOS. In the meantime, please keep recruiting patients into the ENOS 'continue versus stop' part of the trial.
2. The SCAST trial is testing oral candesartan in patients with ischaemic or haemorrhagic stroke. It aimed to recruit 2,500 patients but will cease enrollment this quarter with a total recruitment that will top 2,000. Once again, this means the trial will be somewhat underpowered statistically. We are approaching SCAST sites to see if they would like to join ENOS.

Your Trial Steering Committee believes that it is even more important now that ENOS reaches its target. So, please recruit more patients so that we can, once and for all, determine the best management of BP in acute stroke. In the meantime, if you have any questions or comments about any of the above, please do let me know.

All the very best,

Philip

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Stroke Association Professor of Stroke Medicine
Chief Investigator: ENOS

Trial Paperwork

R&D: please notify your R&D depts of the new end date for ENOS (31 Oct 2013) and forward updated letters to the ENOS Trial Office.
MHRA/MREC: Substantial amendment submitted and approvals are pending.
Contracts: An addendum to extend the end date in Payment Schedule will be sent where needed.

Recruitment to 28 Feb

International	**667**
Australia	**8**
Box Hill, Melbourne	*8*
Canberra	*0*
Canada	**33**
Cape Breton	*1*
Halifax (NC)	*32*
China	**103**
Tian Tan (NC)	*16*
Wenzhou	*87*
Egypt	**8**
Ain Shams Uni (NC)	*8*
Hong Kong	**4**
India	**61**
AIIMS (NC)	*22*
Armed For Med Coll	*1*
Ludhiana, CMC	*30*
Lilavati, LKMM	*8*
Malaysia	**8**
Univer Sains Mlya (NC)	*8*
New Zealand	**43**
Dunedin	*36*
Hawkes Bay (NC)	*3*
Hutt Hospital	*3*
Auckland	*1*
Philippines	**16**
Poland	**103**
Inst Psyc & Neur (NC)	*93*
Military Med Acad	*9*
Hospital Sandomierz	*1*
Republic of Ireland	**4**
Dublin, Tallaght (NC)	*4*
Romania	**66**
Clin Hosp, Oradea	*21*
Fogolyan Kristof Sftu	*22*
Mures County (NC)	*23*
Singapore	**155**
Singapore General	*155*
Spain	**5**
Hospital La Paz (NC)	*1*
Tarragona	*4*
Sri Lanka	**50**
South Colombo	*10*
Univ of Kelaniya (NC)	*40*

UK	1028
Aberdeen	*76*
Antrim Area Hospital, NI	*5*
Barnsley	*18*
Blackpool Victoria	*33*
Borders Melrose	*3*
Chesterfield Royal	*20*
Countess of Chester	*7*
Cumberland Infirm, Carlisle	*1*
Darlington/Bishp Auckland	*69*
Derby Hospitals	*43*
Diana Princess, Grimsby	*5*
Doncaster	*19*
Edinburgh Royal	*7*
Edinburgh Western	*17*
Fairfield General, Bury	*12*
Glasgow Royal Infirmary	*12*
Harrogate District	*9*
James Cook, Middlesbrgh	*9*
John Radcliffe, Oxford	*4*
Kings College London	*4*
Leeds General Infirmary	*9*
Leicester General	*4*
Lincoln County	*65*
Macclesfield DGH	*18*
Monklands Glasgow	*22*
Musgrove Park, Taunton	*1*
New Cross Wolverhmptn	*4*
Newark Hospital	*3*
Newham General	*29*
Ninewells, Dundee	*1*
Northampton General	*3*
Northwick Park, London	*1*
Nottingham City	*197*
Pilgrim Boston	*45*
QMC Nottingham	*23*
Rochdale Infirmary	*6*
Royal Cornwall	*1*
Royal Devon & Exeter	*18*
Royal Hallams Sheffield	*1*
Royal Lancaster	*6*
Royal Liverpool	*3*
Royal Preston	*12*
Royal Victoria, Newcastle	*4*
Scarborough	*7*
Scunthorpe	*2*
Sherwood Forest Hospitals	*7*
Solihull Hospital	*1*
Southport & Ormskirk	*1*
St Marys Isle of Wight	*2*
Staffordshire General	*1*
Stockport Stepping Hill	*20*
Stobhill Glasgow	*4*
Stoke-on-Trent, Royal Inf	*30*
The Royal London	*8*
The Ulster Hospital	*1*
Torbay	*15*
University Hosp, Aintree	*12*
University Hosp, Coventry	*3*
University Hosp, Bristol	*3*
Victoria Hosp Kirkcaldy Fife	*28*
Watford General	*13*
West Cumberand Hosp.	*1*
Western Infirmary, Glasgow	*2*
Yeovil District Hospital	*11*
York Hospital	*5*
Ysbyty Gwynned, Bangor	*1*

Grand Total:

1695

Transfer of CT Scans

We can now only accept CT/MR scan data through the ENOS website scan upload facility. The reason is that we cannot have non-anonymised scans on CD since, in the eventuality that they get lost en route from your hospital to the Trial Coordinating Centre, they will be readable by anyone and therefore are not confidential. Such losses of data would result in disciplinary action, probably against both you as the sender and us as the receiver.

We apologise about the need for this change but the legal position has become very clear and it is now very evident that transfer of unencrypted person-identifiable information on electronic media is expressly forbidden by the NHS. The penalty for breaking the rule is a maximum fine of £500,000, disciplinary action, and reputational damage.

If you find that the upload facility does not work in your institution please discuss this with us and we will need to find a local solution to help you work around the problem.

Any sites currently sending CDs need to try to use the scan upload facility. The easiest method is the Java applet method which can be tested on the Demo website. If the Java applet cannot be used, there is an alternative upload facility, although this takes longer as each file has to be individually identified.

If your centre cannot upload scans online, it may be possible to send encrypted CDs, but we will need to liaise about encryption methods in advance.

If all other options have been ruled out, it may be possible to send film by secure courier. Any queries on CT scans, please email Tanya.Jones@nottingham.ac.uk, Data/Imaging Administrator.

Nurse Consent – UK Only

We have been approached by several collaborators about nurses taking consent for the ENOS trial. As you know, we have promoted this practice and it is explicitly addressed and supported in the Protocol (current version 1.5, section 2.6). To confirm our practice, we recently approached the MHRA about this issue and they have responded with the following:

"The Clinical Trial Regulations refer to the process of informed consent in parts 3, 4 and 5 of Schedule 1. The text in each part states similarly:

"...an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted".
Hence in the UK, provided there is input from the Investigator to the process, the Nurse obtaining consent is acceptable. It is true we generally expect that the Physician is available to ask questions of if the Subject so wishes and/or the Nurse has questions. It is expected that the Physician also has documented evidence of involvement in the determination of eligibility. In your specific case (from the information supplied extracted from the protocol), an Inspector would look to the documentation to provide assurance the protocol was complied with, and in support would expect an appropriate delegation of authority by the Chief/Principal Investigator in advance of staff performing their duties. Our position is not consistent with Inspectors in other Member States who do expect consent to be taken by the Physician, and it is not clear if this impacts your study."

In view of this, we would like to make the following points with respect to ENOS UK:
1. Nurses may take consent into ENOS providing they are suitably trained and local policy permits. The Stroke Research Network, through its Local Research Networks, provides such training; your LRN should be approached if training needs to be provided or updated, and a certificate should state that such training has been received.
2. The Nurses should have consent ticked on the Site Delegation/Signature log.
3. The PI, or another Doctor who is trained on ENOS and is on the site's ENOS Delegation/Signature log, should be available if the patient, relative who is providing proxy consent, or Research Nurse require further information.
4. The PI, or another Doctor (as defined above), should make a comment in the notes on the same or next day that the patient fulfilled the inclusion criteria and that the patient, relative or independent physician, gave consent.
5. If the person taking consent is a therapist (physio, occupational or speech) they must have completed consent training and understand the indications and potential (serious) adverse events for GTN and all antihypertensive drug classes.
6. Non healthcare professionals must not take consent for ENOS.

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Congratulations to....

- Royal Victoria Infirmary, Newcastle, Northwick Park Hospital, Ulster Hospital and Royal Cornwall Hospital, Truro, UK for recruiting their first ENOS patients.
- Mures County Emergency Hospital, Romania, Nottingham City Hospital and Pilgrim Hospital UK for being the Highest Recruiting Centres in the last 90 Days.

*****Recruitment Offer*****

All centres that recruit 3 patients in March will receive a hamper for the wards.

Recent and forthcoming ENOS meetings

UK Teleconference workshop, held 27 January. Next date to be advised.
West Midlands SRN, 22 January. **North West SRN,** 29 January.
India Investigator Meeting, 13 March.
Peninsula SRN, 22 April **Thames SRN,** 23 April **Welsh Stroke Conf**, 25 June.
European Stroke Congress, A joint ENOS/IST-3 Investigator Meeting will be held in Barcelona on Thursday 27 May, early evening. Venue to be advised.

Training for new staff

For investigators that join the ENOS trial at centres after the site initiation visit has been completed, we need them to fax the following to the ENOS Trial Office:

- A signed and dated CV
- GCP certificate
- Updated signature log

There is now a Powerpoint presentation on the ENOS website that new staff need to have read through. Once they receive an ENOS password, the first time they log into the website, the investigator will be asked to confirm that they have completed ENOS training, either attended a site initiation visit or completed the Powerpoint presentation and will work to GCP standards.
NB This question will appear to all ENOS investigators once it has been implemented and everyone will be asked to confirm that they have received trial training. Once this has been ticked as "yes", the question will not appear again. If "no" is ticked, access to randomisation will not be permitted.

Tips of the month

Hospital Event Form wording has changed online:

- On the HE form, question A10 "Result of Carotid Ultrasound" has changed to "Result of carotid scan". We would like to collect all carotid scans, where one has been carried out.

Day 7 Form, question D9 wording has changed online:

- On the Day 7 form, question D9 "Date and time of first GTN patch" has been changed to "Date and time of first GTN patch and/or gauze dressing". We would like this to be answered for **every** patient, whether randomised to GTN or no GTN.

Inclusion/exclusion recent enquiries:

- History of AF is not an exclusion.
- There is no upper limit for diastolic BP.
- Patients on prior antihypertensive medication are eligible, but must be randomised to continue/stop arm of the trial.

Blood pressure:

- Ensure BP is recorded 1-2 hours post patch/gauze dressing placement.
- The three baseline BP readings should be carried out shortly before randomisation.

******Recently Updated Forms******

- Powerpoint presentation, Trial status, Glasgow, Dec 2009
- MHRA substantial amendments, April, June, August, Nov, Dec 2007
- MHRA/REC substantial amendment application form, January 2010
- Safe haven fax documentation, Nottingham University NHS Trust advice, April 2008
- ENOS Trial Office contacts, v1.8, 15 January 2010
- Protocol summary, v1.7
- Site monitoring form v1.9, Site monitoring patient file checklist v1.9

Tip from Investigator who was recently monitored by MHRA – use the monitoring forms above, with one copy of the form in each patient's trial file as an internal check to ensure all the relevant documentation is complete.

ENOS now has 136 centres in 18 countries. More centres are welcome.