Nottingham University Hospitals NHS
NHS Trust

Division of Stroke Medicine
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB
Telephone:01158231768
E-mail:
philip.bath@nottingham.ac.uk

17th December 2008

Nottingham Research Ethics Committee 2
Level 2
1 Standard Court
Park Row
Nottingham
NG1 6GN

Dear Sir/Madam,

**Re: Rapid Intervention with GTN in Hypertensive stroke Trial (RIGHT)**
**REC reference number: 08/H0408/18**

I am pleased to resubmit the revised COREC application form and supporting documents for ethics review for the "Rapid Intervention with GTN in Hypertensive stroke Trial" (RIGHT) trial.

We have addressed all the issues raised by the Nottingham research ethics committee 2 on your letter dated 05.03.2008 in the study protocol and these are summarised as follows.

1. Stroke is a neurological emergency that requires prompt and immediate care. Therefore finding acute interventions that reduce early brain damage to improve outcome from stroke is of major importance. As a result, it is vital to carry out research to identify potential therapeutic strategies that could be implemented during the hyperacute/very early stages of stroke.

   We have performed three randomised controlled phase II studies of glyceryl trinitrate (GTN) in acute stroke, these involving a total of 145 patients. These trials showed that GTN was safe and lowered systolic blood pressure (BP) by an average of ~8% over 24 hours, and with a peak effect of ~12% at 1 hour. GTN did not alter platelet function and therefore may be given to patients with intracerebral haemorrhage. In a separate

study, GTN lowered BP by 10% but had no effect on global/hemispheric/regional cerebral blood flow (assessed using xenon CT) or middle cerebral artery blood flow velocity; further, GTN did not induce cerebral steal or change cerebral perfusion pressure. Of note, these studies included patients with both acute and subacute stroke.

We are now recruiting patients to the ongoing international multicenter "Efficacy of Nitric oxide in Stroke" (ENOS) trial that recruits patients within 48 hours of stroke onset. Currently ENOS trial has recruited 1,114 patients worldwide; the independent Data Monitoring Committee reviews the patient safety data every 6 months and, at the last assessment at the beginning of December 2008 did not identify any safety issues, and recommended that the trial should continue.

Although ENOS allows recruitment of patients between 0.5 and 48 hours post stroke, few patients have been recruited during the first 6 hours. This reflects that the trial is only performed in patients who have been admitted to hospital. We believe the proposed RIGHT will provide further information on the safety and BP effects of GTN in patients with hyperacute stroke. Importantly, we have no evidence that the safety and effects of GTN on BP will be time-dependent so there is no reason to believe that responses will be different in the hyperacute phases as compared with the acute and subacute phases.

2. RIGHT has two specific aims, each dependent on the other. The first is to assess the feasibility of performing trials in the ambulance environment in patients with hyperacute stroke. No such trials have been performed in the UK and only one, albeit non-controlled, trial has been published from the USA. If the 'time is lost brain' adage is correct, then treatments started very early are the ones that are most likely to be effective. There is already excellent evidence that the benefits of thrombolysis for stroke are highly time-dependent; unfortunately thrombolysis cannot be administered for stroke in the ambulance environment because of the prior need for neuroimaging to exclude haemorrhagic stroke. Importantly, ambulance administration of emergency treatment is standard in other acute medical emergencies, including myocardial infarction (MI: aspirin, thrombolysis) and acute asthma (bronchodilators, oxygen). Importantly, GTN is already administered by paramedics to patients with acute MI. To test whether it is possible to perform trials in ambulances, it is necessary to perform a trial, i.e. it would achieve nothing to show that patients could be formally consented to receive standard therapy such as oxygen or fluids if these were going to be given anyway.

   This need to perform a trial in the ambulance to show that it is, or is not, possible to do such trials means that a suitable trial needs to be identified.

Unfortunately, many potential treatments for acute stroke require prior neuroimaging to exclude haemorrhagic stroke.

Such treatments need standard diagnostic criteria thereby allowing an accurate initial diagnosis to be made (e.g. clinical presentation and ECG for MI); ambulance-administered treatment then needs to be tested in clinical trials. Hence, thrombolysis for MI was given 45 minutes earlier if administered in an ambulance than at hospital. Treatments for acute ischaemic stroke (AIS) are not routinely administered prior to hospital since current therapies (e.g. aspirin, alteplase) alter haemostasis and need prior CT/MRI scanning to exclude primary intracerebral haemorrhage (PICH). However, other potential treatments for acute stroke such as neuroprotection and management of physiological disequilibrium (e.g. high blood pressure [BP], hyperglycaemia, pyrexia) do not necessarily need prior neuroimaging and could be delivered prior to hospitalisation. Any benefits of such interventions are likely to be highly time dependent so that pre-hospital administration could considerably increase treatment efficacy through reducing onset to treatment times. A recent study (FASTMag pilot) by Saver in Los Angeles of ambulance administration of intravenous magnesium (a potential neuroprotectant) found that it was possible to enrol, consent, collect basic clinical details, and administer treatment in 20 patients with acute stroke(<12 hours of ictus). The main FASTMag trial (http://www.fastmag.info/) is now running in 1,298 pre-hospital patients from Los Angeles and is funded by NIH/NINDS. This trial has already recruited more than 300 patients to date.

3. We have already updated the inclusion/exclusion criteria in the trial protocol and now women under 55 are excluded from the trial.

If you have any questions on this COREC application form or any other supporting documents please do not hesitate to contact me.

Yours sincerely,

Philip Bath BSc MB BS MD FRCPath FRCP
Stroke Association Professor of Stroke Medicine