NHS
National Research Ethics Service
South East Research Ethics Committee
South East Coast Strategic Health Authority
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ME20 7NJ

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14 October 2008

17 OCT 2008

Professor Philip M. W. Bath
Professor of Stroke Medicine
University of Nottingham
Division of Stroke Medicine,
City Hospital Campus
Nottingham
NG5 1PB

Dear Professor Bath

| | |
|---|---|
| **Full title of study:** | **Safety and tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial** |
| **REC reference number:** | **08/H1102/92** |
| **Protocol number:** | **1.0** |
| **EudraCT number:** | **2007-006749-42** |

The Research Ethics Committee reviewed the above application at the meeting held on 08 October 2008. Thank you for attending to discuss the study.

**Ethical opinion**

The members of the Committee present decided they were unable to give a favourable ethical opinion of the research, for the following reasons:

The main concerns of the Committee were the lack of clarity regarding the risk of bleeding. Although, at the meeting, you advised that a bleed in the brain should be obvious and that the risk is very low for the one month period, the Committee still had concerns that if the patient were at home when the bleeding started they may not realize what was happening and this could be fatal.

a) Further clarification is requested regarding the risks of bleeding.
b) The term "reducing dependency" in the short title may be misleading as the study is not looking at dependency as such. The applicant is asked to consider amending the title.
c) Question 2b regarding the use of blood samples on the filter page of the application form had not been ticked and therefore certain questions relating to the samples will not have appeared on the form.
d) It was felt that the issues in A10 have not been thought through (eg transport for patients and carers if they need to come back), and this needs to be revisited.
e) There were concerns over the risk of patients being rushed into the study, and the Committee requested reassurance that all risks in this respect had been addressed.

f) While the main risk is bleeding, A14 does not pick up on the issue of sensitivity and distress to the participants. This was discussed at the meeting, but the Committee would like further reassurance of how any sensitive issues / distress will be managed by the researcher.

g) Reassurance is needed regarding telephone interviews and how these will be managed as many stroke patients will be unable to use the telephone (eg be unable to speak or be severely disabled).

h) The exclusion criteria in the protocol uses abbreviations of a, c or d. Although most healthcare professionals will understand this, it would be safer to have the terms in full.

i) The application includes the term "enteral access" which is a somewhat obscure term in this context.

j) The Committee would like reassurance that the applicant has a clear understanding of and is compliant with the Mental Capacity Act.

k) The Committee felt it was unacceptable not to have funding for translators especially in view of the greater risk for the Asian population. Provision should be made for these language groups.

l) A34 is very vague on whether participants will receive travel expenses and a clearer explanation is required. All participants and their carers should be offered expenses.

m) The paragraph in A39 is very vague about sharing the data with other researchers and a clearer explanation is requested.

n) The Committee requested to see a copy of the review undertaken by the British Heart Foundation when it became available.

o) The Committee requested to see a copy of the quality of life questionnaire and mood questionnaire which will be part of the 90 day follow up.

p) There is a typo in the second safety measure under A49 which needs to be corrected.

q) The second page (18) of A49 cross references against protocols for other studies. Cross-referencing does not make for the requisite clarity since the Protocol is not available to the whole Committee; full details should therefore be given.

r) A clearer explanation of the criteria for stopping the trial needs to be given under A57 as this is in technical language not readily understood by the lay person.

s) The risk of bleeding in the lay summary (A68) is not portrayed clearly enough and should be revisited.

t) There should be a separate consent form for the genetic study.

u) The GP letter should be accompanied by the PIS.

v) The Committee would like reassurance that the indemnity arrangements for the study will provide adequate cover to meet the potential liability assessed by the sponsor.

**Participant Information Sheet (PIS)**

w) The risk of bleeding to be portrayed very clearly. Specific details need to be given on how participants will know if they have a bleed as this could be fatal.

x) Other information in the protocol, such as the use of antacids, needs to also be in the PIS.

y) It was suggested that the boxes be taken out as this is something of a diversion to the eyes, and may especially affect those with poor sight.

z) The flow chart needs to be made clearer and the boxing to be taken out.

aa) Page 3 needs a clear indication of the frequency of side effects of the three drugs.

bb) The name of the REC needs to be changed.

cc) The exclusion criteria should be included in the PIS, especially given its likely readership

dd) Participants will need to stay still for one hour, which may cause discomfort and this should be clearly explained in the PIS.

I regret to inform you therefore that the application is not approved.

The Committee were very supportive of the study and would welcome a resubmission taking into consideration the Committee's comments.

**Options for further ethical review**

You may submit a new application for ethical review, taking into account the Committee's concerns. You should enter details of this application on the application form and include a copy of this letter, together with a covering letter explaining what changes have been made from the previous application. The application should be booked through the Central Allocation System (CAS) and would be allocated for review in the normal way. You should let CAS know if you would like the application to be reviewed again by this Committee.

Alternatively, you may appeal against the decision of the Committee by seeking a second opinion on this application from another Research Ethics Committee. The appeal would be based on the application form and supporting documentation reviewed by this Committee, without amendment. If you wish to appeal, you should notify the relevant Research Ethics Service manager (see below) in writing within 90 days of the date of this letter. If the appeal is allowed, another REC will be appointed to give a second opinion within 60 days and the second REC will be provided with a copy of the application, together with this letter and other relevant correspondence on the application. You will be notified of the arrangements for the meeting of the second REC and will be able to attend and/or make written representations if you wish to do so.

The contact point for appeals is:

Joan Kirkbride
Acting Head of Operations, England
Head of Operations, North, Midlands and East of England
National Research Ethics Service, National Patient Safety Agency
Darlington Primary Care Trust, Dr Piper House
King Street
Darlington DL3 6JL
joan.kirkbride@nres.npsa.nhs.uk

**Documents reviewed**

The documents reviewed at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| Evidence of Insurance | | 05 August 2008 |
| Request form for authorisation from MHRA | | |
| Participant Consent Form: Independent Physicians | 1.0 | 24 July 2008 |
| Participant Consent Form: Relatives | 1.0 | 24 July 2008 |
| Participant Consent Form | 1.0 | 24 July 2008 |
| Participant Information Sheet: For patients with consent by relative or legal representative | 1.0 | 24 July 2008 |
| Participant Information Sheet: Independent Physicians | 1.0 | 24 July 2008 |
| Participant Information Sheet: Relatives | 1.0 | 24 July 2008 |
| Participant Information Sheet | 1.0 | 24 July 2008 |
| GP/Consultant Information Sheets | 1.0 | 24 July 2008 |
| Letter from Sponsor | | 13 August 2008 |

| | | |
|---|---|---|
| Covering Letter | | 13 August 2008 |
| Protocol | 1.0 | 24 July 2008 |
| Investigator CV | Professor Philip Bath | 13 August 2008 |
| Application | | 13 August 2008 |
| Participant Consent Form: Agreement Form after Relative or Legal Representative | 1.0 | 24 July 2008 |

**Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Professor Eastwood declared a non-specific, non-personal interest in the study. Members agreed that Professor Eastwood could remain in the meeting and contribute to the review of the study.

**Statement of compliance**

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Re-submission/Appeal.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

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|---|---|
| **08/H1102/92** | **Please quote this number on all correspondence** |

Yours sincerely

pp **Dr L. Alan Ruben**
**Chair**

Email: nicki.watts@nhs.net

*Enclosures:* *List of names and professions of members who were present at the meeting and those who submitted written comments*

Copy to: *Mr Paul Cartledge*
*Clinical Trials Unit, MHRA*

## South East Research Ethics Committee

## Attendance at Committee meeting on 08 October 2008

### Committee Members:

| *Name* | *Profession* | *Present* | *Notes* |
|---|---|---|---|
| Dr Dipti Amin | Physician | No | |
| Dr A Bhiman | Consultant Psychiatrist | Yes | |
| Doctor Bob Brecher | Reader in Moral Philosophy | Yes | |
| Professor David Caplin | Physicist | Yes | |
| Professor David Croisdale-Appleby | Professor in Medical Research and Medical Education | Yes | |
| Professor John Eastwood | Consultant Renal Physician | Yes | |
| Dr Alan Fishtal | GP | Yes | |
| Dr Anne Gallagher | Senior Research Fellow (Nurse Member) | Yes | |
| Mr Guy Gardener | Retired Assistant Chief Constable | Yes | |
| Dr Ray Godfrey | Educational Statistician | No | |
| Mrs Vera Hughes | Training Consultant | No | |
| Dr Anton Joseph | Consultant Radiologist | No | |
| Professor Cornelius Katona | Academic Psychiatrist | Yes | |
| Professor Liz Meerabeau | University Professor (Nurse Member) | Yes | |
| Dr L. Alan Ruben | GP | Yes | |
| Mr Roy Sinclair | Pharmacist | Yes | |

### Also in attendance:

| *Name* | *Position (or reason for attending)* |
|---|---|
| Miss Nicki Watts | Co-ordinator |

### Written comments received from:

| *Name* | *Position* |
|---|---|
| Dr Ray Godfrey | Educational Statistician |