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Dr L. Alan Ruben
Chair of South East Research Ethics Committee
South East Coast Strategic Health Authority
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1st December 08. It will (This date change is on our local copy only. Ethics copy is dated 21/OCT/08)
~~21st October 2008~~

| | |
|---|---|
| **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/H1102/112 (new)** |
| **EudraCT number:** | **2007-006749-42** |

Dear Dr Ruben and colleagues,

Following your provisional opinion on the above trial on 12/11/2008, please find enclosed our response. Your letter dated 19/11/08 (also enclosed) listed a number of issues and we will address each one in turn.

a) **Although the application states that the British Heart Foundation have advised that "the Committee did not have any comments that would be helpful", the Committee would still like to see a copy of that report.**

RESPONSE
The application history is slightly complex in that our initial application was made to The Stroke Association (TSA). TSA approved the trial for funding but did not have the funds available to support it. Under an existing agreement with the British Heart Foundation (BHF), they requested that BHF support it, which was agreed. Following your request, we approached TSA and they agreed to share their external reviewers comments, which we now attach. As above, these comments were associated with a positive approval by TSA.

**b) 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.**

RESPONSE
Ms Angela Shone, who supports The University of Nottingham with administration of its sponsor role, has provided the following comments:
"The University of Nottingham fully understands and accepts its obligations towards the participants in clinical trials and has taken out an insurance policy, with a limit of liability set at £10 million as an expectation that this level will meet any costs and compensation set by a judge should there be any claims against the University that are successfully upheld in a court of law. Should any such costs be set higher than this limit then those costs will be met by other means at the University's expense".

c) **The applicant is reminded that he cannot keep samples once this study has been completed unless he applies for an HTA license for a tissue bank to store the samples or submits a further application for ethical approval relating to the tests he wishes to conduct on the samples. The applicant is asked to confirm that he is complying with the HTA.**

RESPONSE
We understand this issue and already have samples from earlier completed studies ruling which are compliant with HTA regulations. The laboratories used for storage at the University of Nottingham already hold a license with the HTA.

**d) Clarification is sought as to why the subgroup analysis is restricted to the main phase**

RESPONSE
The start-up phase is largely designed to analyse safety and the sample size will not be sufficient to enable meaningful and statistically valid subgroup analyses. However, patients enrolled into the start-up phase will be part of the main phase and therefore will contribute subgroup analyses for the trial as a whole. Additionally, the Data Monitoring Committee may study ongoing data in any subgroups they deem important at any time in the trial.

**e) There should be a separate consent form for relatives/legal representatives/etc.**

These consent forms have already been provided and reviewed. We have spoken with Nicki Watts who has confirmed that this point of clarification is a mistake and not required.

**Participant Information Sheet (PIS)**

**f) A specific point from p 11 of the protocol should be included to advise patients using enteric-coated aspirin against ingesting antacids simultaneously to avoid premature drug release.**

RESPONSE
This has been added to the PIS and highlighted for your attention.

**g) It states that if the participant experiences any bleeding after they are discharged they should report it immediately to their GP or NHS Direct. This was discussed at the meeting and the Committee felt that in the first instance the participant should be advised to contact the study doctor, and in the second instance their GP. It was not felt appropriate for participants to contact NHS Direct.**

RESPONSE
The information sheet now conveys this point on page 4 and reads as follows: "If you do notice any bleeding, then you must report it immediately as a large bleed can be fatal if it is not treated. If you are is still in hospital, you should tell the research doctor or the doctors and nurses on the ward. If you are out of hospital you should tell the research doctor or the GP. Bleeding can present itself in a number of ways and you should report any of the following symptoms…"

**h) A lay summary of the results needs to be offered to participants.**

RESPONSE
This will be provided and is explained in the PIS. The results will be displayed on the trial website (www.tardistrial.org/) for trial participants to view.

We hope that the above responses are to your satisfaction and that the trial now meets with your approval.

Yours sincerely

Professor Philip Bath, MD FRCP
Professor of Stroke Medicine

Enclosed:

- Reviewer comments from The Stroke Association
- Patient Information Sheet (version 1.2) and consent form (version 1.2)
- Relative Information Sheet (version 1.2) and consent form (version 1.2)
- Patient Information Sheet (for patients with consent by relative or legal representative) (version 1.2) and consent form (version 1.2)
- Independent Physician Information Sheet (version 1.2) and consent form (version 1.2)