The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

22nd December 2011

School of Clinical Sciences
Division of Stroke
Clinical Sciences Building
City Hospital Campus
Hucknall Road
Nottingham
NG5 1PB
t: +44 (0)115 823 1765
f: +44 (0)115 823 1767
www.nottingham.ac.uk/scs/divisions/stroke
Head of Department :
Philip M W Bath

Chairman
South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall, Aylesford
Kent
ME20 7NJ

Re: Substantial Protocol Amendment: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke

Long title: Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack: a randomised controlled trial

EudraCT No: 2007-006749-42
REC Reference number: 08/H1102/112
Sponsor Reference: SA06/11 (please quote)

Dear Chairman and colleagues,

This clinical trial received a favourable opinion letter on 09 January 2009 and 635 patients have been recruited to date.

I am writing regarding a substantial amendment to the TARDIS trial protocol. The updated version 1.3 of the protocol consists primarily of the following changes in the running of the trial:

1. The National Institute of Clinical Excellence (NICE) guidelines for secondary prevention of vascular disease (TA210) was updated in December 2010. It recommends clopidogrel monotherapy after stroke and dual therapy with aspirin and dipyridamole after transient ischaemic attack for secondary prevention. So the trial will now test intensive

antiplatelet therapy (combined aspirin, dipyridamole and clopidogrel) versus the guideline treatment (dual aspirin and dipyridamole or clopidogrel monotherapy) in high-risk acute stroke and TIA patients.

2. All the three antiplatelet drugs (aspirin, dipyridamole and clopidogrel) will be considered as investigational medicinal products (previously only clopidogrel).

3. The trial will aim to recruit approximately 1000 patients in the start-up phase. This will seamlessly then run into the main phase without interruption to recruit a further 3,100 patients following successful funding.

4. The Transcranial Doppler study is now being discontinued.

The updated documents with tracked changes are enclosed.

We request that you kindly review and approve these changes to the conduct of the trial. I will be grateful if you could kindly approve these changes in the conduct of the trial.

Enclosures:

1. **Substantial Amendment Application Form.**
2. **Summary of changes Protocol Version 1.3**
3. **Protocol V 1.3 20 December 2011 with tracked changes**
4. **Protocol V 1.3 20 December 2011 final document**
5. **Updated supporting documents- information sheets and consent forms with and without tracked changes**

Please contact me for any further information you may require.

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

Substantial Amendment Notification Form (Cf. Section 3.7.b of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial*[1])

NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION

For official use:

Date of receiving the request :	Grounds for non acceptance/ negative opinion **:** ❑ Date :
Date of start of procedure:	Authorisation/ positive opinion **:** ❑ Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application ❑ Date :

To be filled in by the applicant:

This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

A TYPE OF NOTIFICATION

A.1 Member State in which the substantial amendment is being submitted:	
A.2 Notification for authorisation to the competent authority:	**No**
A.3 Notification for an opinion to the ethics committee:	**Yes**

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1 Does the substantial amendment concern several trials involving the same IMP?[2]	No
B.1.1 If yes repeat this section as necessary.	

B.2 Eudract number:2007-006749-42

B.3 Full title of the trial :Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack: a randomised controlled trial

B.4 Sponsor's protocol code number, version, and date: 31350 and 08093, version 1.3, 20th December 2011

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1 Sponsor	
C.1.1	Organisation: University of Nottingham
C.1.2	Name of person to contact: Mr Paul Cartledge
C.1.3	Address : Head of Research Grants and Contracts, Research Innovation Services, University of Nottingham
C.1.4	Telephone number : 0115 9515679
C.1.5	Fax number : 0115 9513633
C.1.6	e-mail: paul.cartledge@nottingham.ac.uk

C.2 Legal representative[3] of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)	
C.2.1	Organisation:
C.2.2	Name of person to contact:
C.2.3	Address :
C.2.4	Telephone number :
C.2.5	Fax Number:
C.2.6	e-mail:

D APPLICANT IDENTIFICATION (please tick the appropriate box)

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.
2 Cf. Section 3.7. of the detailed guidance CT-1.
3 As stated in Article 19 of Directive 2001/20/EC.

D.1	Request for the competent authority	
D.1.1	Sponsor	❑
D.1.2	Legal representative of the sponsor	❑
D.1.3	Person or organisation authorised by the sponsor to make the application.	
D.1.4	Complete below:	
D.1.4.1	Organisation :	
D.1.4.2	Name of person to contact : Address : Telephone number :Fax number :	
D.1.4.3	E-mail:	

D.2	Request for the Ethics Committee	
D.2.1	Sponsor	❑
D.2.2	Legal representative of the sponsor	❑
D.2.3	Person or organisation authorised by the sponsor to make the application.	YES
D.2.4	Investigator in charge of the application if applicable[4]:	
	• Co-ordinating investigator (for multicentre trial)	❑
	• Principal investigator (for single centre trial):	❑
D.2.5	Complete below	
D.2.5.1	Organisation :University of Nottingham	
D.2.5.2	Name :Professor Philip Bath	
D.2.5.3	Address :Division of Stroke, Clinical Sciences Building, City Hospital Campus, Nottingham NG5 1PB	
D.2.5.4	Telephone number :0115 8231765	
D.2.5.5	Fax number :0115 8231767	
D.2.6	E-mail :philip.bath@nottingham.ac.uk	

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1 Sponsor's substantial amendment code number, version, date for the clinical trial concerned:
(SA06/11, protocol V 1.3, 20th December 2011)

E.2	Type of substantial amendment	
E.2.1	**Amendment to information in the CT application form**	Yes
E.2.2	**Amendment to the protocol**	Yes
E.2.3	**Amendment to other documents appended to the initial application form**	Yes
E.2.3.1	If yes specify:	
E.2.4	**Amendment to other documents or information:**	No
E.2.4.1	If yes specify:	
E.2.5	**This amendment concerns mainly urgent safety measures already implemented[5]**	no
E.2.6	**This amendment is to notify a temporary halt of the trial[6]**	no
E.2.7	**This amendment is to request the restart of the trial[7]**	no

4 According to national legislation.
5 Cf. Section 3.9. of the detailed guidance CT-1.
6 Cf. Section 3.10. of the detailed guidance CT-1.
7 Cf. Section 3.10. of the detailed guidance CT-1.

E.3	Reasons for the substantial amendment:	
E.3.1	**Changes in safety or integrity of trial subjects**	**no**
E.3.2	**Changes in interpretation of scientific documents/value of the trial**	**no**
E.3.3	**Changes in quality of IMP(s)**	**no**
E.3.4	**Changes in conduct or management of the trial**	**yes**
E.3.5	**Change or addition of principal investigator(s), co-ordinating investigator**	**no**
E.3.6	**Change/addition of site(s)**	**no**
E.3.7	**Other change**	**no**
E.3.7.1	**If yes, specify:**	
E.3.8	**Other case**	**yes ❑ no ❑**
E.3.8.1	**If yes, specify**	

E.4	Information on temporary halt of trial[8]	
E.4.1	**Date of temporary halt** (YYYY/MM/DD)	
E.4.2	**Recruitment has been stopped**	yes ❑ no ❑
E.4.3	**Treatment has been stopped**	yes ❑ no ❑
E.4.4	Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment ( )	
E.4.5	**Briefly describe (free text)**:	

- Justification for a temporary halt of the trial
- The proposed management of patients receiving treatment at time of the halt *(free text)*.

The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text)*.

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9] *(free text)*:

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment
Summary of changes with old and new wording attached as a separated document titled 'TARDIS Protocol Version 1.3, Summary of Changes'		**1. Trial will test intensive antiplatelet therapy with aspirin, dipyridamole and clopidogrel versus guideline therapy (combined aspirin and dipyridamole or clopidogrel)** **2. All the three drugs (Aspirin, Dipyridamole and Clopidogrel) will be considered as IMPs** **3. TCD sub study is discontinued** **4. Background to the study has been updated with current literature.**

G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

G.1	Type of change

[8] Cf. Section 3.10. of the detailed guidance CT-1.

[9] Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

G.1.1 **Addition of a new site**
G.1.1.1 **Principal investigator** (provide details below)
G.1.1.1.1 Given name
G.1.1.1.2 Middle name (if applicable)
G.1.1.1.3 Family name
G.1.1.1.4 Qualifications (MD……..)
G.1.1.1.5 Professional address
G.1.2 **Removal of an existing site**
G.1.2.1 **Principal investigator** (provide details below)
G.1.2.1.1 Given name
G.1.2.1.2 Middle name (if applicable)
G.1.2.1.3 Family name
G.1.2.1.4 Qualifications (MD……..)
G.1.2.1.5 Professional address
G.1.3 **Change of co-ordinating investigator** (provide details below of the new coordinating investigator)
G.1.3.1 Given name
G.1.3.2 Middle name
G.1.3.3 Family name
G.1.3.4 Qualification (MD…….)
G.1.3.5 Professional address
G.1.3.6 Indicate the name of the previous co-ordinating investigator:
G.1.4 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)
G.1.4.1 Given name
G.1.4.2 Middle name
G.1.4.3 Family name
G.1.4.4 Qualifications (MD……..)
G.1.4.5 Professional address
G.1.4.6 Indicate the name of the previous principal investigator:

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

H.1 Change of e-mail contact for feedback on application*

H.2 Change to request to receive an .xml copy of CTA data ❑ yes ❑ no
H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? ❑ yes ❑ no
H.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):
H.2.2 Do you want to receive this via password protected link(s)[10]? ❑ yes ❑ no

If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s)

H.2.3 Do you want to stop messages to an email for which they were previously requested? ❑ yes ❑ no
H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:

(*This will only come into effect from the time at which the request is processed in EudraCT).

I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

I.1 Cover letter	Yes
I.2 Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)	Yes
I.3 Entire new version of the document[11]	No
I.4 Supporting information	Yes
I.5 Revised .xml file and copy of initial application form with amended data highlighted	Yes
I.6 Comments on any novel aspect of the amendment if any :	

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

[10] This requires a EudraLink account. (See https://eudract.ema.europa.eu/ for details)
[11] Cf. Section 3.7.c. of the detailed guidance CT-1.

J.1	I hereby confirm that/ confirm on behalf of the sponsor that (delete which is not applicable) • The above information given on this request is correct; • The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and • It is reasonable for the proposed amendment to be undertaken.

J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY(as stated in section D.1): ☑	
J.2.1	Signature [12]:
J.2.2	Print name :
J.2.3	Date :

J.3	**APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE** (as stated in section D.2): ❑
J.3.1	Signature [13]:
J.3.2	Print name:
J.3.3	Date :

[12] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
[13] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.

NRES Committee London - South East

Room 4W/12
4th Floor West
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Telephone: 020 331 17254

03 May 2012

Professor Philip M. W. Bath
Professor of Stroke Medicine
University of Nottingham
Division of Stroke Medicine – Research Dept
Clinical Sciences Building
City Hospital Campus
Hucknall Road
Nottingham
NG5 1PB

Dear Professor Bath

Study title:	**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:	**08/H1102/112**
Protocol number:	**31350**
EudraCT number:	**2007-006749-42**
REC Amendment number:	**AM18 (our reference)**
Amendment number:	**SA06/11, Protocol V1.3, 20/12/2011**
Amendment date:	**22 December 2011**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
TARDIS GP Letter	1.2 (tracked changes)	20 December 2011

TARDIS GP Letter	1.2	20 December 2011
Annex 1 - Clinical Trial Application Form		
Participant Consent Form: TARDIS: Proxy Relative Consent Form	1.5 (tracked changes)	20 December 2011
Participant Consent Form: TARDIS: Proxy Relative Consent Form	1.5	20 December 2011
Participant Consent Form: TARDIS: Agreement Form after Proxy Relative or Legal Representative Consent	1.5 (tracked changes)	20 December 2011
Participant Consent Form: TARDIS Agreement Form After Proxy Relative or Legal Representative Consent	1.5	20 December 2011
Participant Information Sheet: TARDIS Relative Information Sheet	1.5	20 December 2011
Participant Information Sheet: TARDIS Participant Information Sheet after RIS	1.5 (tracked changes)	20 December 2011
Participant Information Sheet: TARDIS Participant Information Sheet	1.5	20 December 2011
Participant Information Sheet: TARDIS Participant Information Sheet	1.5 (tracked changes)	20 November 2011
European Commission Notification of Substantial Amendment Form	SA06/11, Protocol V1.3, 20/12/2011	22 December 2011
Covering Letter		
Substantial Protocol Amendment Summary of Changes Version 1.3		
Participant Consent Form: TARDIS Patient Consent Form	1.5 (Tracked Changes)	20 December 2011
Participant Consent Form: TARDIS Patient Consent Form	1.5	20 December 2011
Participant Consent Form: TARDIS Independent Physician Consent Form	1.5 (tracked changes)	20 December 2011
Participant Consent Form: TARDIS Independent Physician Consent Form	1.5	20 December 2011
Participant Information Sheet: TARDIS - Independent Physician Information Sheet	1.5 (tracked changes)	10 February 2011
Protocol	1.3	20 December 2011
Protocol	1.3 (tracked changes)	20 December 2011
Participant Information Sheet: TARDIS Independent Physician Information Sheet	1.5	10 February 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

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 and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H1102/112:	**Please quote this number on all correspondence**

Yours sincerely

pp
Professor David Caplin
Chair

Email: Janhoi.McGregor@imperial.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Mr Paul Cartledge, Research Innovation Services, University of Nottingham

NRES Committee London - South East

Sub-Committee of the REC

Name	*Profession*	*Capacity*
Professor David Caplin	Physicist	Lay
Mr Roy Sinclair	Pharmacist	Expert