

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 : <input type="checkbox"/> Date :
Date of start of procedure:	Authorisation/ positive opinion : <input type="checkbox"/> Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application <input type="checkbox"/> 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:	UK	
A.2 Notification for authorisation to the competent authority:		<input type="checkbox"/> NO
A.3 Notification for an opinion to the ethics committee:		<input type="checkbox"/> 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 <input type="checkbox"/>
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 tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial.

B.4 Sponsor's protocol code number, version, and date: 31350/08093 TARDIS Protocol V1.2 20/5/09

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, University of Nottingham, Research Innovation Services, King's Meadow Campus, Lenton Lane, Nottingham NG7 2NR
C.1.4 Telephone number : 0115 951 5679
C.1.5 Fax number : 0115 951 3633
C.1.6 e-mail: paul.cartledge@nottingham.ac.uk

C.2 Legal representative³ 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	NO
D.1.2	Legal representative of the sponsor	<input type="checkbox"/>
D.1.3	Person or organisation authorised by the sponsor to make the application.	<input type="checkbox"/>
D.1.4	Complete below:	
D.1.4.1	Organisation : University of Nottingham	
D.1.4.2	Name of person to contact : Prof Philip Bath	
D.1.4.3	Address : Clinical Sciences Building, Div Stroke, city Hospital Campus, Hucknall Rd, Nottingham NG5 1PB	
D.1.4.4	Telephone number : 0115 8231765	
D.1.4.5	Fax number : 0115 8231767	
D.1.4.6	E-mail : margaret.adrian@nottingham.ac.uk	

D.2 Request for the Ethics Committee		
D.2.1	Sponsor	YES
D.2.2	Legal representative of the sponsor	<input type="checkbox"/>
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)	YES
	• Principal investigator (for single centre trial):	<input type="checkbox"/>
D.2.5	Complete below	
D.2.5.1	Organisation : University of Nottingham	
D.2.5.2	Name : Prof Philip Bath	
D.2.5.3	Address : Clinical Sciences Building, Div of Stroke, c/o Nottingham City Hospital, Hucknall Rd, 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: (SA05/11)

E.2 Type of substantial amendment		
E.2.1	Amendment to information in the CT application form	no <input type="checkbox"/>
E.2.2	Amendment to the protocol	no <input type="checkbox"/>
E.2.3	Amendment to other documents appended to the initial application form	no <input type="checkbox"/>
E.2.3.1	If yes specify:	
E.2.4	Amendment to other documents or information:	no <input type="checkbox"/>
E.2.4.1	If yes specify:	
E.2.5	This amendment concerns mainly urgent safety measures already implemented⁵	no <input type="checkbox"/>
E.2.6	This amendment is to notify a temporary halt of the trial⁶	no <input type="checkbox"/>
E.2.7	This amendment is to request the restart of the trial⁷	no <input type="checkbox"/>

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 <input type="checkbox"/>
E.3.2	Changes in interpretation of scientific documents/value of the trial	no <input type="checkbox"/>
E.3.3	Changes in quality of IMP(s)	no <input type="checkbox"/>
E.3.4	Changes in conduct or management of the trial	no <input type="checkbox"/>
E.3.5	Change or addition of principal investigator(s), co-ordinating investigator	YES <input type="checkbox"/>
E.3.6	Change/addition of site(s)	no <input type="checkbox"/>
E.3.7	Other change	no <input type="checkbox"/>
E.3.7.1	If yes, specify:	
E.3.8	Other case	n/a
E.3.8.1	If yes, specify	

E.4 Information on temporary halt of trial⁸ N/A		
E.4.1	Date of temporary halt (YYYY/MM/DD)	
E.4.2	Recruitment has been stopped	yes <input type="checkbox"/> no <input type="checkbox"/>
E.4.3	Treatment has been stopped	yes <input type="checkbox"/> no <input type="checkbox"/>
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): <ul style="list-style-type: none"> Justification for a temporary halt of the trial The proposed management of patients receiving treatment at time of the halt (<i>free text</i>). The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product (<i>free text</i>).	

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT⁹ (*free text*):

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment
		<ul style="list-style-type: none"> Change of PI at an existing site (Basildon). If funding for Main Trial unsuccessful: <ul style="list-style-type: none"> Extend length of startup period from 36 to 43 months. Increase recruitment for the startup period to a maximum of 1000.

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

<p>G.1 Type of change</p> <p>G.1.1 Addition of a new site (<i>change of Trust name only, same PI</i>)</p> <p>G.1.1.1 Principal investigator (provide details below)</p> <p>G.1.1.1.1 Given name</p> <p>G.1.1.1.2 Middle name (if applicable)</p> <p>G.1.1.1.3 Family name</p> <p>G.1.1.1.4 Qualifications (MD.....)</p> <p>G.1.1.1.5 Professional address.</p> <p>G.1.1.1.6 .</p> <p>G.1.1.1.7</p> <p>G.1.2 Removal of an existing site</p> <p>G.1.2.1 Principal investigator (provide details below)</p> <p>G.1.2.1.1 Given name</p> <p>G.1.2.1.2 Middle name (if applicable)</p> <p>G.1.2.1.3 Family name</p> <p>G.1.2.1.4 Qualifications (MD.....)</p> <p>G.1.2.1.5 Professional address</p> <p>G.1.2.1.6</p> <p>G.1.3 Change of co-ordinating investigator (provide details below of the new coordinating investigator)</p> <p>G.1.3.1 Given name</p> <p>G.1.3.2 Family name</p> <p>G.1.3.3 Qualification (MD.....) ...</p> <p>G.1.3.4 Professional address</p> <p>G.1.3.5 Indicate the name of the previous co-ordinating investigator:</p> <p>G.1.4</p> <p>G.1.5</p> <p>G.1.6 Change of principal investigator at an existing site (provide details below of the new principal investigator)</p> <p>G.1.6.1 Given name Udayaraj</p> <p>G.1.6.2 Middle name</p> <p>G.1.6.3 Family name Umasankar</p> <p>G.1.6.4 Qualifications (MD) MBBS MRCP LAB ECFMG</p> <p>G.1.6.5 Professional address Basildon & Thurrock University Hospitals, Nethermayne, Basildon, SS16 5NL</p> <p>G.1.6.6</p> <p>G.1.6.7 Indicate the name of the previous principal investigator: Dr Huwez</p> <p>G.1.6.8</p> <p>G.1.7</p>

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	<input type="checkbox"/> no
H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT?	<input type="checkbox"/> 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 ?	<input type="checkbox"/> yes <input type="checkbox"/> 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) | <input type="checkbox"/> |
| I.3 Entire new version of the document ¹¹ | <input type="checkbox"/> |
| I.4 Supporting information | <input type="checkbox"/> |
| I.5 Revised .xml file and copy of initial application form with amended data highlighted | <input type="checkbox"/> |
| I.6 Comments on any novel aspect of the amendment if any | |

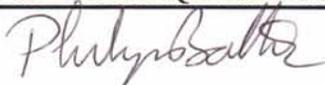
J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

- J.1 I hereby confirm on behalf of the sponsor that
- 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):
 NO

- J.2.1 Signature¹²:
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): YES

- J.3.1 Signature¹³: 
J.3.2 Print name: **P BALTHUS**
J.3.3 Date : **25/11/11**

¹¹ Cf. Section 3.7.c. of the detailed guidance CT-1.

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.



Health Research Authority

NRES Committee London - South East

Room 4W/10
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Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Tel: 02033110105
Fax: n/a

24 January 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

Amendment number:

Amendment date: 25 November 2011

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
European Commission Notification of Substantial Amendment Form		25 November 2011
Covering Letter		25 November 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

P.P.



Prof. David Caplin
Chair

E-mail: danyal.enver@nhs.net

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

*Copy to: N/A. R&D contact not specified in database.
Mr Paul Cartledge*

NRES Committee London - South East

Attendance at Sub-Committee of the REC meeting on 16 December 2011