



The University of  
**Nottingham**

UNITED KINGDOM · CHINA · MALAYSIA

Faculty of Medicine and Health Sciences  
School of Medicine

Division of Clinical Neuroscience  
Stroke

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City Hospital Campus  
Hucknall Road

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[http://www.nottingham.ac.uk/research/  
groups/stroke/index.aspx](http://www.nottingham.ac.uk/research/groups/stroke/index.aspx)

Head of Division/Head of Stroke  
Stroke Association Professor of Stroke Medicine:  
Professor P M W Bath

31 January 2014

Dr L A Ruben  
Chair of South East Research Ethics Committee  
South East Coast Strategic Health Authority  
Preston Hall  
Aylesford  
Kent  
ME20 7NJ

Your reference: 08/H1102/112  
Eudract Number: 2007-006749-42  
Protocol No: 31350 & 08093 V1.4 Protocol 26/02/2013  
Amendment Reference: SA01/14

Dear Dr Ruben and colleagues

**Trial Title: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke**

Please find enclosed a substantial amendment for the above trial to update an existing letter to GPs and to add two new letters to GPs and patients.

Yours sincerely

Sally Utton  
TARDIS Trial Manager

Encs: Notice of Substantial amendment form  
GP letter at Baseline v1.3, 23/1/14  
GP letter at Day 35 v1.0, 23/1/14  
GP letter at Day 90 v1.0, 23/1/14

cc: RGS, University of Nottingham



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31 January 2014

Information Processing Unit  
Area 6, MHRA  
151 Buckingham Palace Road  
Victoria  
London  
SW1W 9SZ

Eudract Number: 2007-006749-42  
Protocol No: 31350 & 08093 V1.4 Protocol 26/02/2013  
Reference: SA01/14

Dear Sir or Madam

**Trial Title: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke**

Please find enclosed a substantial amendment for the above trial to update an existing letter to GPs and add two new letters to GPs and patients.

We look forward to receiving your acknowledgement and approval.

Yours faithfully

Sally Utton  
TARDIS Trial Manager

Encs: Notice of Substantial amendment form  
GP letter at Baseline v1.3, 23/1/14  
GP letter at Day 35 v1.0, 23/1/14  
GP letter at Day 90 v1.0, 23/1/14

cc: RGS, University of Nottingham

**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*<sup>1</sup>)**

**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 of start of procedure:	Date : <input type="checkbox"/>
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Authorisation/ positive opinion : <input type="checkbox"/>
	Date : <input type="checkbox"/>
	Withdrawal of amendment application <input type="checkbox"/>
	Date : <input type="checkbox"/>

*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**

<b>A.1 Member State in which the substantial amendment is being submitted:</b>	UK	
<b>A.2 Notification for authorisation to the competent authority:</b>		<input type="checkbox"/> yes
<b>A.3 Notification for an opinion to the ethics committee:</b>		<input type="checkbox"/> yes

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

<b>B.1 Does the substantial amendment concern several trials involving the same IMP?<sup>2</sup></b>	<input type="checkbox"/> no
B.1.1 If yes repeat this section as necessary.	

<b>B.2 Eudract number:</b> 2007-006749-42
<b>B.3 Full title of the trial :</b> Safety and efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack (TIA): a randomised controlled trial <b>Sponsor's protocol code number, version, and date:</b> 31350 and 08093 TARDIS Protocol V1.4 26/02/13

**C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST**

<b>C.1 Sponsor</b>
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: <a href="mailto:paul.cartledge@nottingham.ac.uk">paul.cartledge@nottingham.ac.uk</a>

<b>C.2 Legal representative<sup>3</sup> of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)</b>
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 :

<sup>1</sup> OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.

<sup>2</sup> Cf. Section 3.7. of the detailed guidance CT-1.

<sup>3</sup> As stated in Article 19 of Directive 2001/20/EC.

C.2.6 e-mail:

**D APPLICANT IDENTIFICATION (please tick the appropriate box)**

**D.1 Request for the competent authority**

- D.1.1 Sponsor YES  
D.1.2 Legal representative of the sponsor   
D.1.3 Person or organisation authorised by the sponsor to make the application. YES  
D.1.4 Complete below:  
D.1.4.1 Organisation : University of Nottingham  
D.1.4.2 Name of person to contact : Sally Utton  
D.1.4.3 Address : Division of Stroke, Clinical Sciences Building, City Hospital Campus, Hucknall Road, Nottingham NG5 1PB  
D.1.4.4 Telephone number : 0115 823 0287  
D.1.4.5 Fax number : 0115 823 1771  
D.1.4.6 E-mail Sally.utton@nottingham.ac.uk

**D.2 Request for the Ethics Committee**

- D.2.1 Sponsor YES  
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<sup>4</sup>:  
• Co-ordinating investigator (for multicentre trial) YES  
• Principal investigator (for single centre trial):   
D.2.5 Complete below  
D.2.5.1 Organisation : University of Nottingham  
D.2.5.2 Name : Mrs Sally Utton  
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 823 0287  
D.2.5.5 Fax number : 0115 823 1771  
D.2.6 E-mail : sally.utton@nottingham.ac.uk

**E SUBSTANTIAL AMENDMENT IDENTIFICATION**

**E.1 Sponsor's substantial amendment code number, version, date for the clinical trial concerned: (SA01/14)**

**E.2 Type of substantial amendment**

- E.2.1 Amendment to information in the CT application form no  
E.2.2 Amendment to the protocol no   
E.2.3 Amendment to other documents appended to the initial application form no   
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<sup>5</sup> no   
E.2.6 This amendment is to notify a temporary halt of the trial<sup>6</sup> no   
E.2.7 This amendment is to request the restart of the trial<sup>7</sup> no

<sup>4</sup> According to national legislation.

<sup>5</sup> Cf. Section 3.9. of the detailed guidance CT-1.

<sup>6</sup> Cf. Section 3.10. of the detailed guidance CT-1.

<sup>7</sup> Cf. Section 3.10. of the detailed guidance CT-1.

<b>E.3</b>	<b>Reasons for the substantial amendment:</b>	
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	YES <input type="checkbox"/>
E.3.5	Change or addition of principal investigator(s), co-ordinating investigator	no <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	
E.3.8.1	If yes, specify	

<b>E.4</b>	<b>Information on temporary halt of trial<sup>8</sup></b>	N/A
E.4.1	Date of temporary halt (YYYY/MM/DD)	
E.4.2	Recruitment has been stopped	no <input type="checkbox"/>
E.4.3	Treatment has been stopped	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	<b>Briefly describe (free text):</b>	
	<ul style="list-style-type: none"> <li>Justification for a temporary halt of the trial</li> <li>The proposed management of patients receiving treatment at time of the halt (<i>free text</i>).</li> </ul> <p>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>).</p>	

**F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT<sup>9</sup> (*free text*):**

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment
Update GP letter from sites to GPs to improve on patient safety.	V1.3, 23/1/14. New wording is highlighted.	To make it clearer that the trial treatment should stop at Day 35.

<sup>8</sup> Cf. Section 3.10. of the detailed guidance CT-1.

<sup>9</sup> 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**

**G.1 Type of change**

**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.....)

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.1.2.1.6**

**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.....)

Professional address

**G.1.3.5** 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** Qualification (MD.....)

Professional address Indicate the name of the previous co-ordinating 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

no

**H.2.1** Do you want a .xml file copy of the CTA form data saved on EudraCT?

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)<sup>10</sup>?

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?

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)**

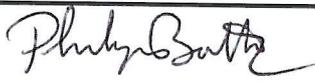
*Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).*

- |   |                          |
|---|--------------------------|
| 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 <sup>11</sup>  | <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  | no                       |
| I.6 Comments on any novel aspect of the amendment if any  |                          |

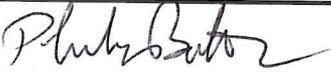
**J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE**

- 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): YES**

J.2.1 Signature<sup>12</sup>:  PHILIP BATH  
 J.2.2 Print name: PHILIP BATH  
 J.2.3 Date: 31/1/14

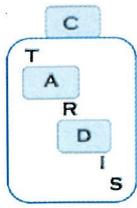
**J.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (as stated in section D.2): YES**

J.3.1 Signature<sup>13</sup>:  PHILIP BATH  
 J.3.2 Print name: PHILIP BATH  
 J.3.3 Date: 31/1/14

<sup>11</sup> Cf. Section 3.7.c. of the detailed guidance CT-1.

<sup>12</sup> On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.

<sup>13</sup> On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.



GP Address

### INFORMATION FOR THE GENERAL PRACTITIONER AT BASELINE

Dear Colleague,

Your patient [insert name]

living at [insert address]

has agreed to participate in the TARDIS trial, a randomised controlled trial of intensive antiplatelet therapy with combined clopidogrel, aspirin and dipyridamole versus current guideline treatment in high risk patients with recent ischaemic stroke.

Stroke recurrence is greatest immediately after stroke or TIA; existing prevention strategies (antithrombotic, lipid/blood pressure lowering, endarterectomy) reduce, not abolish, further events. Dual antiplatelet therapy, such as aspirin and dipyridamole, is superior to aspirin monotherapy. Triple antiplatelet therapy reduces MI and death in patients with coronary disease. We have shown that it is feasible to give triple therapy (aspirin, clopidogrel, dipyridamole) to patients with ischemic stroke/TIA. We will assess the efficacy, safety, tolerability and feasibility of intensive antiplatelet therapy with combined clopidogrel, aspirin and dipyridamole versus current guideline therapy (aspirin and dipyridamole or clopidogrel) given for 1 month in patients with acute stroke/TIA (i.e. at high risk of recurrence).

Your patient has been randomised to receive [insert] for 30 days.

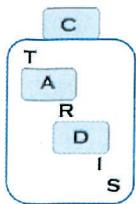
Patients should go back to guideline therapy (combined Aspirin and Dipyridamole, or Clopidogrel alone) after trial treatment period completes at 30 days. **Please ensure that your patient has completed their trial treatment by [insert date], and after this date, your patient goes back onto guideline therapy, as per your local practice.**

The primary outcome is the level of dependency at 90 days, and safety at 1 month; secondary outcomes include serious adverse events, vascular events, death, and platelet function.

Our research team will follow up your patient over a period of three months. If problems arise in connection with this study please do not hesitate to contact us (tel \_\_\_\_\_). A copy of the patient information sheet has been provided for you.

Yours sincerely,

Investigator's name here



TARDIS Trial Office  
Stroke, Division of Clinical Neuroscience  
University of Nottingham  
Clinical Sciences Building  
City Hospital Campus  
Hucknall Road  
Nottingham  
NG5 1PB

GP Address

**INFORMATION FOR THE GENERAL PRACTITIONER AT DAY 35**

Dear Colleague,

Your patient [insert name]

and living at [insert address]

is participating in the TARDIS trial, a randomised controlled trial of intensive antiplatelet therapy (combined aspirin, clopidogrel and dipyridamole) versus current guideline treatment in high risk patients with recent ischaemic stroke.

Your patient was randomised to receive [insert] for 30 days from [insert date of randomisation].

When this patients' day 35 follow up visit was conducted, the database has recorded that they are taking still taking [insert] Aspirin and Clopidogrel/Aspirin, Clopidogrel and Dipyridamole/or no antiplatelets). After the treatment period of 30 days, patients should go back to guideline therapy (combined Aspirin and Dipyridamole, or Clopidogrel alone). Please ensure that your patient is switched as soon as possible to guideline therapy as per your local practice. This is important to reduce the risk of bleeding (if AC/C), recurrent stroke (if none).

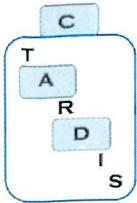
If problems arise in connection with this study, please do not hesitate to contact us (Tel: +44 (0) 115 8231770).

Yours sincerely,

Professor Philip Bath  
TARDIS Chief Investigator

cc. Local recruiting site [insert]

Patient [insert name]



TARDIS Trial Office  
Stroke, Division of Clinical Neuroscience  
University of Nottingham  
Clinical Sciences Building  
City Hospital Campus  
Hucknall Road  
Nottingham  
NG5 1PB

GP Address

### **INFORMATION FOR THE GENERAL PRACTITIONER AT DAY 90**

Dear Colleague,

Your patient [insert name]

and living at [insert address]

is participating in the TARDIS trial, a randomised controlled trial of intensive antiplatelet therapy with combined clopidogrel, aspirin and dipyridamole versus current guideline treatment in high risk patients with recent ischaemic stroke.

Your patient was randomised to receive [insert] for 30 days from [insert date of randomisation].

When this patients' day 90 telephone follow up visit was conducted, the database has recorded that they are still taking [insert] Aspirin and Clopidogrel/Aspirin, Clopidogrel and Dipyridamole/or no antiplatelets). After the treatment period of 30 days, patients should go back to guideline therapy (combined Aspirin and Dipyridamole, or Clopidogrel alone). Please ensure that your patient is switched as soon as possible to guideline therapy as per your local practice. This is important to reduce the risk of bleeding (if AC/C), recurrent stroke (if none).

If problems arise in connection with this study, please do not hesitate to contact us (Tel: +44 (0) 115 8231770).

Yours sincerely,

Professor Philip Bath  
TARDIS Chief Investigator

cc. Local recruiting site [insert]

Patient [insert name]