



The University of
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School of Clinical Sciences
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Head of Department :
Philip M W Bath

21 December 2012

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 V1.2 Protocol 20/05/2009

Dear Dr Ruben and colleagues

Trial Title: Safety and tolerability of clopidogrel when added to aspirin and dipyridamole in high risk patients with recent ischaemic stroke: a randomised controlled trial

Please find enclosed a substantial amendment for the above trial to change Principal Investigators and add new centres. We look forward to receiving your approval letter.

Yours sincerely

Sally Utton
TARDIS Trial Manager

Encs: SA03/12

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 efficacy of intensive versus guideline antiplatelet therapy in high risk patients with recent ischaemic stroke or transient ischaemic attack (TIA): a randomised controlled trial
Sponsor's protocol code number, version, and date: 08093 TARDIS Protocol V1.3 20/12/2011

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, 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 :

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.

C.2.6 e-mail:

D APPLICANT IDENTIFICATION (please tick the appropriate box)

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. | |
| D.1.4 Complete below: | |
| D.1.4.1 Organisation : | |
| D.1.4.2 Name of person to contact : | |
| D.1.4.3 Address : | |
| D.1.4.4 Telephone number : | |
| D.1.4.5 Fax number : | |
| D.1.4.6 E-mail | |

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: (SA03/12)

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 | 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 implemented ⁵ | no <input type="checkbox"/> |
| E.2.6 This amendment is to notify a temporary halt of the trial ⁶ | no <input type="checkbox"/> |
| E.2.7 This amendment is to request the restart of the trial ⁷ | 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)	YES <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
		Change of PI and addition of new PIs at various sites.

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

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 Bernard

G.1.1.1.2 Middle name (if applicable)

G.1.1.1.3 Family name Esi

G.1.1.1.4 Qualifications (MD.....) MD

Professional address. County Durham & Darlington NHS Foundation Trust

University Hospital North Durham Durham DH1 5TW

G.1.2 Addition of a new site

G.1.2.1 Principal investigator (provide details below)

G.1.2.1.1 Given name Matthew

G.1.2.1.2 Middle name (if applicable)

G.1.2.1.3 Family name Burn

G.1.2.1.4 Qualifications (MD.....) MD

Professional address. Buckinghamshire Healthcare Trust Wycombe General Hospital Queen Alexander Road

High Wycombe Buckinghamshire HP11 2TT

G.1.2.2 Principal investigator (provide details below)

G.1.2.2.1 Given name Ibrahim

G.1.2.2.2 Middle name (if applicable)

G.1.2.2.3 Family name Memon

G.1.2.2.4 Qualifications (MD.....) MD

Professional address. Heart of England NHS Foundation Trust Good Hope Hospital Rectory Road

Sutton Coldfield Birmingham B75 7RR

G.1.2.3 Principal investigator (provide details below)

G.1.2.3.1 Given name David

G.1.2.3.2 Middle name (if applicable)

G.1.2.3.3 Family name Broughton

G.1.2.3.4 Qualifications (MD.....) MD

Professional address. South Tees Hospitals NHS Foundation Trust James Cook University Hospital

Marton Road Middlesbrough TS4 3BW

G.1.2.4 Principal investigator (provide details below)

G.1.2.4.1 Given name Ruth

G.1.2.4.2 Middle name (if applicable)

G.1.2.4.3 Family name Davies

G.1.2.4.4 Qualifications (MD.....) MD

Professional address. Wirral University Teaching Hospitals NHS Foundation Trust Arrowe Park Hospital

Upton Wirral CH49 5PE

G.1.2.5 Principal investigator (provide details below)

G.1.2.5.1 Given name Peter

G.1.2.5.2 Middle name (if applicable)

G.1.2.5.3 Family name Owusu-Ahyei

G.1.2.5.4 Qualifications (MD.....) MD

Professional address. Peterborough and Stamford Hospitals NHS Foundation Trust Peterborough City

Hospital Bretton Lane Peterborough PE3 9GZ

G.1.2.6 Principal investigator (provide details below)

G.1.2.6.1 Given name Janet

G.1.2.6.2 Middle name (if applicable)

G.1.2.6.3 Family name Putterill

G.1.2.6.4 Qualifications (MD.....) MD
Professional address. Epsom & St Helier University Hospitals Trust Epsom General Hospital Dorking Road
Epsom Surrey KT18 7EG

G.1.2.7 **Principal investigator** (provide details below)

G.1.2.7.1 Given name Richard

G.1.2.7.2 Middle name (if applicable)

G.1.2.7.3 Family name Perry

G.1.2.7.4 Qualifications (MD.....) MD

Professional address. University College London Hospitals NHS Foundation Trust University College Hospital
235 Euston Road London NW1 2BU

G.1.2.8 **Principal investigator** (provide details below)

G.1.2.8.1 Given name Karim

G.1.2.8.2 Middle name (if applicable)

G.1.2.8.3 Family name Mahawish

G.1.2.8.4 Qualifications (MD.....) MD

Professional address. Warrington and Halton Hospitals NHS Foundation Trust Warrington Hospital
Lovely Lane Warrington WA5 1QG

G.1.2.9 **Principal investigator** (provide details below)

G.1.2.9.1 Given name David

G.1.2.9.2 Middle name (if applicable)

G.1.2.9.3 Family name Bruce

G.1.2.9.4 Qualifications (MD.....) MD

Professional address. North Tees and Hartlepool NHS Trust University Hospital of Hartlepool
Hartlepool TS24 9AH

G.1.2.10 **Principal investigator** (provide details below)

G.1.2.10.1 Given name Bartlomiej

G.1.2.10.2 Middle name (if applicable)

G.1.2.10.3 Family name Piechowski-Jozwiak

G.1.2.10.4 Qualifications (MD.....) MD

Professional address. South London Healthcare NHS Trust Princess Royal University Site Farnborough
Common Orpington Kent BR6 8ND

G.1.2.11 **Principal investigator** (provide details below)

G.1.2.11.1 Given name Charlie

G.1.2.11.2 Middle name (if applicable)

G.1.2.11.3 Family name Davie

G.1.2.11.4 Qualifications (MD.....) MD

Professional address. The Royal Free Hampstead NHS Trust Pond Street,
London, NW3 2QG

G.1.2.12 **Principal investigator** (provide details below)

G.1.2.12.1 Given name Kneale

G.1.2.12.2 Middle name (if applicable)

G.1.2.12.3 Family name Metcalfe

G.1.2.12.4 Qualifications (MD.....) MD

Professional address. Norfolk and Norwich University Hospitals NHS Foundation Trust
Norfolk and Norwich University Hospital Colney Lane Norwich NR4 7UY

G.1.2.13 **Principal investigator** (provide details below)

G.1.2.13.1 Given name Raj

G.1.2.13.2 Middle name (if applicable)

G.1.2.13.3 Family name Shekhar

G.1.2.13.4 Qualifications (MD.....) MD

Professional address. The Queen Elizabeth Hospital Kings Lynn NHS Trust Gayton road
King's Lynn PE30 4ET

G.1.2.14 Principal investigator (provide details below)

G.1.2.14.1 Given name Khalid

G.1.2.14.2 Middle name (if applicable)

G.1.2.14.3 Family name Javaid

G.1.2.14.4 Qualifications (MD.....) MD

Professional address. Walsall Healthcare NHS Trust Walsall manor Hospital Moat Road
Walsall West Midlands WS2 9PS

G.1.2.15 Principal investigator (provide details below)

G.1.2.15.1 Given name Azlisham

G.1.2.15.2 Middle name (if applicable)

G.1.2.15.3 Family name Mohd Nor

G.1.2.15.4 Qualifications (MD.....) MD

Professional address. Plymouth Hospitals NHS Trust Derriford Road Crownhill, Plymouth, Devon
PL6 8DH

G.1.2.16 Principal investigator (provide details below)

G.1.2.16.1 Given name Elio

G.1.2.16.2 Middle name (if applicable)

G.1.2.16.3 Family name Giallombardo

G.1.2.16.4 Qualifications (MD.....) MD

Professional address Hampshire Hospitals NHS Foundation Trust Basingstoke and North Hampshire
Hospital Aldermaston Road Basingstoke Hampshire RG24 9NA

G.1.2.17 Principal investigator (provide details below)

G.1.2.17.1 Given name Harbans

G.1.2.17.2 Middle name (if applicable)

G.1.2.17.3 Family name Bhakri

G.1.2.17.4 Qualifications (MD.....) MD

Professional address Weston Area Health NHS Trust Weston General Hospital Grange Road
Uphill Weston-super-Mare North Somerset BS23 4TQ

G.1.2.18 Principal investigator (provide details below)

G.1.2.18.1 Given name Abul

G.1.2.18.2 Middle name (if applicable)

G.1.2.18.3 Family name Azim

G.1.2.18.4 Qualifications (MD.....) MD

Professional address West Suffolk Hospital NHS Trust West Suffolk Hospital Hardwick Lane
Bury St Edmunds Suffolk IP33 2QZ

G.1.3 Removal of an existing site

G.1.3.1 Principal investigator (provide details below)

G.1.3.1.1 Given name

G.1.3.1.2 Middle name (if applicable)

G.1.3.1.3 Family name

G.1.3.1.4 Qualifications (MD.....) MD

G.1.3.1.5 Professional address

G.1.3.1.6

G.1.4 Change of co-ordinating investigator (provide details below of the new coordinating 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

G.1.4.5 Indicate the name of the previous co-ordinating investigator:

G.1.4.6

G.1.5 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)

G.1.5.1 Given name Peter

G.1.5.2 Middle name

G.1.5.3 Family name Wilkinson

G.1.5.4 Qualification (MD.....) MD

Professional address Ashford and St Peter's Hospitals NHS Foundation Trust Guildford Road Chertsey Surrey KT16 OPZ

G.1.5.5 Indicate the name of the previous co-ordinating investigator: Dr Baskar Mandal

G.1.6 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)

G.1.6.1 Given name Anand

G.1.6.2 Middle name

G.1.6.3 Family name Nair

G.1.6.4 Qualification (MD.....) MD

Professional address Calderdale and Huddersfield NHS Foundation Trust Calderdale Royal Hospital Salterhebble Halifax HX3 0PW

Indicate the name of the previous co-ordinating investigator: Dr Irfan Shakir

G.1.7 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)

G.1.7.1 Given name Peter

G.1.7.2 Middle name

G.1.7.3 Family name Murphy

G.1.7.4 Qualification (MD.....) MD

Professional address University Hospitals Bristol NHS Foundation Trust Bristol Royal Infirmary Bristol BS2 8HW

Indicate the name of the previous co-ordinating investigator: Dr Julie Dovey

G.1.8 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)

G.1.8.1 Given name Timothy

G.1.8.2 Middle name

G.1.8.3 Family name England

G.1.8.4 Qualification (MD.....) MD

Professional address Derby Hospitals NHS Foundation Trust, Derby, DE22 3DT

Indicate the name of the previous co-ordinating investigator: Dr Khulood Muhiddin

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)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)	<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	YES
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 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): YES

J.3.1 Signature ¹³:

J.3.2 Print name:

J.3.3 Date :

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.

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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).

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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	YES
I.6 Comments on any novel aspect of the amendment if any	

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

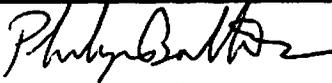
J.1 I hereby confirm on behalf of the sponsor that

- 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: PHILIP BATH
J.3.3 Date : 3/1/13

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.