

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 COMMUNITY

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:	Withdrawal of amendment application <input type="checkbox"/> Date:
Ethics committee registration number of the trial:	

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 checked="" type="checkbox"/>
A.3 Notification for an opinion to the ethics committee:	<input type="checkbox"/>
A.4 Notification for information only¹:	<input type="checkbox"/>
A.4.1 To the competent authority	<input type="checkbox"/>
A.4.2 To the Ethics committee	<input type="checkbox"/>

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?	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
B.1.1 If yes repeat this section as necessary.	

B.2 EudraCT number:	2007-006660-30
B.3 Full title of the trial :	Contemporary Heart Failure Management : A Randomised, Placebo-Controlled Cross-Over Trial to Measure the Effects of Low-Dose Digoxin on Haemodynamics and Symptoms in Patients with Heart Failure
B.4 Sponsor's protocol code number, version, and date:	RO730, Version 2, 9 November 2009

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1 Sponsor	
C.1.1 Organisation:	Hull and East Yorkshire Hospitals NHS Trust
C.1.2 Name of person to contact:	James Illingworth
C.1.3 Address :	R&D Manager R&D Office 12, Daisy Building, Castle Hill Hospital, Cottingham, HU16 5JQ
C.1.4 Telephone number :	01482 461 903
C.1.5 Fax number :	01482 461 886
C.1.6 e-mail:	james.illingworth@hey.nhs.uk

¹ For substantial amendments to information that only the CA has previously assessed (e.g. quality data in most of the MS), the sponsor should not only submit the amendment to the CA but also inform the ethics committee that they have made the notification indicating that it is "for information only". Similarly, the sponsor should inform the CA of any notification of a substantial amendment to information which was previously only assessed by the ethics committee (e.g. facilities for the trial).

C.2	Legal representative² of the sponsor in the Community for the purpose of this trial (if different from the sponsor)
C.2.1	Organisation: Not Applicable
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)

D.1	Request for the competent authority
D.1.1	Sponsor <input type="checkbox"/>
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 checked="" type="checkbox"/>
D.1.4	Complete below:
D.1.4.1	Organisation : University of Hull
D.1.4.2	Name of person to contact : Dr Damien Cullington
D.1.5	Address : Floor 1, Daisy Building, Castle Hill Hospital, Cottingham, HU16 5JQ
D.1.5.1	Telephone number : 01482 461 801
D.1.5.2	Fax number : 01482 461 779
D.1.5.3	E-mail : damien.cullington@hey.nhs.uk

D.2	Request for the Ethics Committee
D.2.1	Sponsor <input type="checkbox"/>
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. <input checked="" type="checkbox"/>
D.2.4	Investigator in charge of the application if applicable ³ :
	• Co-ordinating investigator (for multicentre trial) <input type="checkbox"/>
	• Principal investigator (for single centre trial): <input checked="" type="checkbox"/>
D.2.5	Complete below
D.2.5.1	Organisation : University of Hull
D.2.5.2	Name : Dr Damien Cullington
D.2.5.3	Address : Floor 1, Daisy Building, Castle Hill Hospital, Cottingham, HU16 5JQ
D.2.5.4	Telephone number : 01482 461 801
D.2.5.5	Fax number : 01482 461 779
D.2.6	E-mail : damien.cullington@hey.nhs.uk

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1	Sponsor's substantial amendment code number, version, date for the clinical trial concerned: Substantial amendment version 2, 09.11.09
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² As stated in Article 19 of Directive 2001/20/EC.

³ According to national legislation.

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

E.3 Reasons for the substantial amendment:			
E.3.1	Changes in safety or integrity of trial subjects	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.2	Changes in interpretation of scientific documents/value of the trial	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.3	Changes in quality of IMP(s)	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.4	Changes in conduct or management of the trial	yes <input checked="" type="checkbox"/>	no <input type="checkbox"/>
E.3.5	Change or addition of principal investigator(s), co-ordinating investigator	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.6	Change of sponsor, legal representative, applicant	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.7	Change/addition of site(s)	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.8	Change in transfer of major trial related duties	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.8.1	If yes, specify:		
E.3.9	Other change	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.9.1	If yes, specify:		
E.3.10	Other case	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.3.10.1	If yes, specify		

E.4 Information on temporary halt of trial			
E.4.1	Date of temporary halt (YYYY/MM/DD) 23 October 2009		
E.4.2	Recruitment has been stopped	yes <input checked="" type="checkbox"/>	no <input type="checkbox"/>
E.4.3	Treatment has been stopped	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.4.4	Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment NONE		
E.4.5	What is (are) the reason(s) for the temporary halt?		
E.4.5.1	Safety	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.4.5.2	Lack of efficacy	yes <input type="checkbox"/>	no <input checked="" type="checkbox"/>
E.4.5.3	Other	yes <input checked="" type="checkbox"/>	no <input type="checkbox"/>
E.4.5.3.1	If yes to other, specify : Inability to recruit patients with current inclusion criteria		
E.4.6	Briefly describe (free text): One of the entry criteria was the requirement of patients to have a 3 rd heart sound measured using an acoustic cardiogram machine. After screening 200 patients only 20 patients were found with this feature. After failing other inclusion criteria too few patients were found to be suitable and changes have been made to the entry criteria.		
	• Justification for a temporary halt of the trial		
	• The proposed management of patients receiving treatment at time of the halt (<i>free text</i>): N/A		
	• 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>): N/A		

F REASONS FOR SUBSTANTIAL AMENDMENT (*one or two sentences*):

The entry requirement for a 3rd heart sound measured using acoustic cardiography was too restrictive for trial entry and was significantly limiting recruitment plus the general applicability of results to be utilised for future patient care.

G BRIEF DESCRIPTION OF THE CHANGES (*free text*):

The entry criteria for the study have been broadened and the requirement for patients to have a 3rd heart sound has now been dropped. We intend to select symptomatic heart failure patients with a NTproBNP level >150 pmol/L instead. This should substantially improve the number of patients suitable for trial entry and select a cohort of patients who are at greater risk of their co-morbid illness who may benefit from optimisation of medical therapy. We have added an additional non-invasive, painless test of heart function which will be performed while the patient is at rest and during exercise. No other changes have been made to the study protocol. We request that the trial can be recommenced in light of these alterations.

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

H.1 Type of change

H.1.1 Addition of a new site

H.1.1.1 **Principal investigator** (provide details below)

H.1.1.1.1 Given name

H.1.1.1.2 Middle name (if applicable)

H.1.1.1.3 Family name

H.1.1.1.4 Qualifications (MD.....)

H.1.1.1.5 Professional address

H.1.2 Removal of an existing site

H.1.2.1 **Principal investigator** (provide details below)

H.1.2.1.1 Given name

H.1.2.1.2 Middle name (if applicable)

H.1.2.1.3 Family name

H.1.2.1.4 Qualifications (MD.....)

H.1.2.1.5 Professional address

H.1.3 Change of co-ordinating investigator (provide details below of the new coordinating investigator)

H.1.3.1 Given name

H.1.3.2 Middle name

H.1.3.3 Family name

H.1.3.4 Qualification (MD.....)

H.1.3.5 Professional address

H.1.3.6 Indicate the name of the previous co-ordinating investigator:

H.1.4 Change of principal investigator at an existing site (provide details below of the new principal investigator)

H.1.4.1 Given name

H.1.4.2 Middle name

H.1.4.3 Family name

H.1.4.4 Qualifications (MD.....)

H.1.4.5 Professional address

H.1.4.6 Indicate the name of the previous principal investigator:

I CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

I.1 Change of e-mail contact for feedback on application*	
I.2 Change to request to receive an .xml copy of CTA data	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
I.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT?	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
I.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):	
I.2.2 Do you want to receive this via password protected link(s) ⁴ ?	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
If you answer no to question I.2.2 the .xml file will be transmitted by less secure e-mail link(s)	
I.2.3 Do you want to stop messages to an email for which they were previously requested?	yes <input type="checkbox"/> no <input checked="" type="checkbox"/>
I.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).	

J LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM

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).

J.1 Covering letter stating the type of amendment and the reason(s)	<input checked="" type="checkbox"/>
J.2 Summary of the proposed amendment	<input checked="" type="checkbox"/>
J.3 List of modified documents (identity, version, date)	<input checked="" type="checkbox"/>
J.4 If applicable, pages with previous and new wording	<input checked="" type="checkbox"/>
J.5 Supportive information	<input type="checkbox"/>
J.6 Revised .xml file and copy of initial application form with amended data highlighted	<input checked="" type="checkbox"/>
J.7 Comments on any novel aspect of the amendment if any :	
N/A	

⁴ This requires a EudraLink account. (See www.eudract.emea.eu.int for details)

K SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

K.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.

K.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY(as stated in section C.1):

K.2.1 Signature⁵:

K.2.2 Print name : Damien Cullington

K.2.3 Date : 11 November 2009

K.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (as stated in section C.2):

K.3.1 Signature⁶:

K.3.2 Print name: Damien Cullington

K.3.3 Date : 11 November 2009

⁵ On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.

⁶ On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.