

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 type="checkbox"/>
A.3 Notification for an opinion to the ethics committee:	<input checked="" type="checkbox"/>
A.4 Notification for information only¹:	<input type="checkbox"/>
A.4.1 To the competent authority	<input checked="" 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:	2004-000991-15
B.3 Full title of the trial :	ASCEND: A Study of Cardiovascular Events in Diabetes. A randomised 2x2 factorial study of aspirin versus placebo, and of omega-3 fatty acid supplementation versus placebo, for primary prevention of cardiovascular events in people with diabetes.
B.4 Sponsor's protocol code number, version, and date:	CTSUASCEND, version 8.0_010207, 2007-02-01

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1 Sponsor	
C.1.1 Organisation:	University of Oxford
C.1.2 Name of person to contact:	Jane Armitage
C.1.3 Address :	Clinical Trial Service Unit Richard Doll Building Old Road Campus Oxford, OX3 7LF
C.1.4 Telephone number :	01865 743888
C.1.5 Fax number :	01865 743981
C.1.6 e-mail:	jane.armitage@ctsuo.ox.ac.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:
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 Oxford
D.1.4.2	Name of person to contact :	Jane Armitage
D.1.5	Address :	Clinical Trial Service Unit Richard Doll Building Old Road Campus Oxford. OX3 7LF
D.1.5.1	Telephone number :	01865 743888
D.1.5.2	Fax number :	01865 743981
D.1.5.3	E-mail	jane.armitage@ctsuo.ox.ac.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 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 Oxford
D.2.5.2	Name :	Jane Armitage
D.2.5.3	Address :	Clinical Trial Service Unit Richard Doll Building Old Road Campus Oxford, OX3 7LF
D.2.5.4	Telephone number :	01865 743888
D.2.5.5	Fax number :	01865 743981
D.2.6	E-mail :	jane.armitage@ctsuo.ox.ac.uk

E SUBSTANTIAL AMENDMENT IDENTIFICATION

² As stated in Article 19 of Directive 2001/20/EC.

³ According to national legislation.

E.1 Sponsor's substantial amendment code number, version, date for the clinical trial concerned:

CTSUASCEND2, version 8.0 010207, 2007-02-01

E.2 Type of substantial amendment

- | | | | |
|---------|---|---|--|
| E.2.1 | Amendment to information in the CT application form | yes <input type="checkbox"/> | no <input checked="" 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: Changes required to patient information leaflet, participant invitation letter and letter to GP after participant has returned screening questionnaire. | | |
| 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 type="checkbox"/> | no <input checked="" 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) | | |
| 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 | What is (are) the reason(s) for the temporary halt? | | |
| E.4.5.1 | Safety | yes <input type="checkbox"/> | no <input type="checkbox"/> |
| E.4.5.2 | Lack of efficacy | yes <input type="checkbox"/> | no <input type="checkbox"/> |
| E.4.5.3 | Other | yes <input type="checkbox"/> | no <input type="checkbox"/> |
| E.4.5.3.1 | If yes to other, specify : | | |
| E.4.6 | Briefly describe (free text): | | |
| | <ul style="list-style-type: none">Justification for a temporary halt of the trialThe 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 REASONS FOR SUBSTANTIAL AMENDMENT (one or two sentences):

Recruitment of participants into ASCEND started in March 2005 and has been mainly via locally-held diabetes registers. However, the response rate has been lower than anticipated and, in order to identify the large number of people required to randomize at least 10,000 into this study, more flexible recruitment methods are required.

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

In addition to providing data from locally-held diabetes registers (from which participant invitations may be generated), hospital collaborators and general practitioners/practice nurses will have the option to offer standard "invitation packs" to potentially eligible participants when they are seen for routine care in their clinic. These packs will contain a patient information leaflet, screening questionnaire (with consent form attached) and freepost envelope for return of the questionnaire to the coordinating centre. Randomised participants will also be given the opportunity to recommend any friend or relative they think may be eligible and interested in participating in the study and potential participants may volunteer themselves if they hear about the study from some other route (e.g. via the study website).

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 ☐ no ☐

I.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? yes ☐ no ☐

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 ☐ no ☐

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 ☐ no ☐

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="checked" type="checkbox"/>
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J.2 Summary of the proposed amendment	<input checked="" type="checkbox"/>
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J.3 List of modified documents (identity, version, date)

J.4 If applicable, pages with previous and new wording																								
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J.5 Supportive information

J.6 Revised .xml file and copy of initial application form with amended data highlighted

J.7 Comments on any novel aspect of the amendment if any :

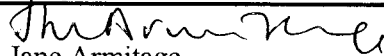
⁴ This requires a EudraLink account. (See www.eudract.emea.eu.int for details)

K SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

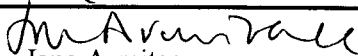
K.1 I hereby confirm that/ confirm on behalf of the sponsor that (delete which is not applicable)

- 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 Signature ⁵: 
K.2.2 Print name : Jane Armitage
K.2.3 Date : 1 Feb 2007

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

K.3.1 Signature ⁶: 
K.3.2 Print name: Jane Armitage
K.3.3 Date : 1 Feb 2007

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.