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 **:** ☐ Date :
Date of start of procedure:	Authorisation/ positive opinion **:** ☐ Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application ☐ 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:	
A.2 Notification for authorisation to the competent authority:	☐
A.3 Notification for an opinion to the ethics committee:	**X**

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] yes ☐ no **X**

B.1.1 If yes repeat this section as necessary.

B.2 Eudract number: 2007-003798-16

B.3 Full title of the trial : AML 17 - A Programme Development in Younger Patients with Acute Myeloid Leukaemia and high Risk Myelodysplastic syndrome

B.4 Sponsor's protocol code number, version, and date: Version 8.0 November 2012

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1	**Sponsor**	
C.1.1	Organisation:	Cardiff University
C.1.2	Name of person to contact:	Dr Kathy Pittard-Davies
C.1.3	Address :	University College of Medicine Heath Park Cardiff
C.1.4	Telephone number :	029 20743262
C.1.5	Fax number :	029 20748267
C.1.6	e-mail:	DaviesKP2@cf.ac.uk

C.2 Legal representative[3] **of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)**

C.2.1 Organisation: Cardiff University

C.2.2 Name of person to contact: Prof AK Burnett

C.2.3 Address : Department of Haematology, School of Medicine
Heath Park, Cardiff

C.2.4 Telephone number : 029 20742375

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.2.5	Fax number : 029 20744655
C.2.6	e-mail: BurnettAK@cardiff.ac.uk
C.2.7	

D APPLICANT IDENTIFICATION (please tick the appropriate box)

D.1	**Request for the competent authority**	
D.1.1	Sponsor	☐
D.1.2	Legal representative of the sponsor	☐
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	☐
D.2.2	Legal representative of the sponsor	X
D.2.3	Person or organisation authorised by the sponsor to make the application.	☐
D.2.4	Investigator in charge of the application if applicable[4]:	☐
	• Co-ordinating investigator (for multicentre trial)	☐
	• Principal investigator (for single centre trial):	☐
D.2.5	Complete below	
D.2.5.1	Organisation : Cardiff University	
D.2.5.2	Name : Prof AK Burnett	
D.2.5.3	Address : Department of Haematology, School of Medicine Heath Park, Cardiff,	
D.2.5.4	Telephone number : 029 20742375	
D.2.5.5	Fax number : 029 20744655	
D.2.6	E-mail : BurnettAK@cardiff.ac.uk	

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1	**Sponsor's substantial amendment code number, version, date for the clinical trial concerned: AML 17 Protocol Version 8.0 dated November 2012**

E.2	**Type of substantial amendment**	
E.2.1	**Amendment to information in the CT application form**	yes X no ☐
E.2.2	**Amendment to the protocol**	yes X no ☐
E.2.3	**Amendment to other documents appended to the initial application form**	yes X no ☐
E.2.3.1	If yes specify: PIS 1 and PIS 2	
E.2.4	**Amendment to other documents or information:**	yes ☐ no X
E.2.4.1	If yes specify:	
E.2.5	**This amendment concerns mainly urgent safety measures already implemented[5]**	yes☐ no X
E.2.6	**This amendment is to notify a temporary halt of the trial[6]**	yes ☐ no X
E.2.7	**This amendment is to request the restart of the trial[7]**	yes ☐ no X

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**	**yes** ☐ **no** X
E.3.2	**Changes in interpretation of scientific documents/value of the trial**	**yes X no** ☐
E.3.3	**Changes in quality of IMP(s)**	**yes** ☐ **no** X
E.3.4	**Changes in conduct or management of the trial**	**yes** ☐ **no** X
E.3.5	**Change or addition of principal investigator(s), co-ordinating investigator**	**yes** X **no** ☐
E.3.6	**Change/addition of site(s)**	**yes** ☐ **no** X
E.3.7	**Other change**	**yes** ☐ **no** ☐
E.3.7.1	**If yes, specify:**	
E.3.8	**Other case**	**yes** ☐ **no** ☐
E.3.8.1	**If yes, specify**	

E.4	Information on temporary halt of trial[8]	
E.4.1	**Date of temporary halt** (YYYY/MM/DD)	
E.4.2	**Recruitment has been stopped**	yes ☐ no ☐
E.4.3	**Treatment has been stopped**	yes ☐ no ☐
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)**:	

- Justification for a temporary halt of the trial
- The proposed management of patients receiving treatment at time of the halt *(free text).*

The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text).*

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9] *(free text)***:**

In June 2011 the AML17 randomisation was amended and approved from a five way randomisation to a 2 way randomisation, the paediatric community have since decided that no children under the age of 16 years will participate in the AML 17 trial therefore all reference to the children randomisation has been removed.

The CEP701/placebo treatment for eligible FLT3+ patients has reached its target accrual and therefore this randomisation arm has been closed to recruitment, details of the treatment have been removed.

The protocol provides for allogeneic transplantation for all adult patients who have an HLA-matched sibling or volunteer unrelated donor and who are designated to have a high risk score or a FLT3+/NPM1⁻ genotype. Recent maturing data suggests that patients who have intermediate risk defined by the risk score who are >40 years will benefit from a Reduced Intensity allograft from a matched sibling donor. Patients who are not high risk or favourable risk (Core Binding Factor) leukaemias are defined as intermediate risk and will be randomised to the 3 versus 4 comparison. Patients in this group who are >40 years of age should be considered for a Reduced Intensity Allograft (RIC) transplant if fully matched sibling donor is available. Investigators will be informed about eligible patients.

The Data monitoring Committee and the Trial Steering Group recommended that the M-tor randomisation be closed and patients discontinue treatment as the Everolimus has shown little or no benefit.

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment
Please see attached document titled AML17 protocol		

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.

amendments: Version 7.2 to Version 8.0 November 2012 which shows all changes in the protocol		

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……..)

G.1.1.1.5 Professional address; **Addition of a new site**

G.1.1.2 **Principal investigator** (provide details below)

G.1.1.2.1 Given name

G.1.1.2.2 Middle name (if applicable)

G.1.1.2.3 Family name

G.1.1.2.4 Qualifications (MD……..)

Professional address

Addition of a new site

G.1.1.3**Principal investigator** (provide details below)

G.1.1.3.1 Given name

G.1.1.3.2 Middle name (if applicable)

G.1.1.3.3 Family name

G.1.1.3.4 Qualifications (MD……..)

Professional address

Addition of a new site

G.1.1.4**Principal investigator** (provide details below)

G.1.1.4.1 Given name

G.1.1.4.2 Middle name (if applicable)

G.1.1.4.3 Family name

G.1.1.4.4 Qualifications (MD……..)

G.1.1.4.5 Professional address

Addition of a new site

G.1.1.5**Principal investigator** (provide details below)

G.1.1.5.1 Given name

G.1.1.5.2 Middle name (if applicable)

G.1.1.5.3 Family name

G.1.1.5.4 Qualifications (MD……..)

G.1.2 Professional address

Addition of a new site

G.1.1.6**Principal investigator** (provide details below)

G.1.1.6.1 Given name

G.1.1.6.2 Middle name (if applicable)

G.1.1.6.3 Family name

G.1.1.6.4 Qualifications (MD……..)

G.1.1.7 Professional address

G.1.1.8

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……..)
G.1.1.1.5 Professional address

Removal of an existing 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……..)
G.1.1.1.5 Professional address

G.1.2 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)

G.1.2.1	Given name	Andrew
G.1.2.2	Middle name	
G.1.2.3	Family name	Fletcher
G.1.2.4	Qualifications (MD……..)	MBchB,FRCPath,MRCPCH
G.1.2.5	Professional address	Chesterfield Royal Hospital Calow Chesterfield S44 5BL

Indicate the name of the previous principal investigator: Dr Robert Cutting

G.1.3 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)
G.1.3.1 Given name
G.1.3.2 Middle name
G.1.3.3 Family name
G.1.3.4 Qualifications (MD……..)
G.1.3.5 Professional address

Indicate the name of the previous principal 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 Qualifications (MD……..)
G.1.4.5 Professional address

Indicate the name of the previous principal investigator:

G.1.2
G.1.4.6 Given name
G.1.4.7 Middle name
G.1.4.8 Family name
G.1.4.9 Qualifications (MD……..)

G.1.4.10 Professional address
G.1.4.11 Indicate the name of the previous principal investigator:
Change of principal investigator at an existing site (provide details below of the new principal investigator)
G.1.4.12 Given name
G.1.4.13 Middle name
G.1.4.14 Family name
G.1.4.15 Qualifications (MD……..)
G.1.4.16 Professional address
G.1.4.17

G.1.4.18 Indicate the name of the previous principal investigator:

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
G.1.5.2 Middle name
G.1.5.3 Family name
G.1.5.4 Qualifications (MD……..)
G.1.1.1.6 Professional address

G.1.6 Indicate the name of the previous principal investigator:

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
G.1.7.2 Middle name
G.1.7.3 Family name
G.1.7.4 Qualifications (MD……..)
G.1.7.5 Professional address

Indicate the name of the previous principal investigator:

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
G.1.8.2 Middle name
G.1.8.3 Family name
G.1.8.4 Qualifications (MD……..)
G.1.8.5 Professional address

G.1.1.2 Indicate the name of the previous principal investigator:
G.1.2.1

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

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 X

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 X

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**	X
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)**	**X**
I.3	**Entire new version of the document**[11]	☐
I.4	**Supporting information**	X
I.5	**Revised .xml file and copy of initial application form with amended data highlighted**	X
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 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.

J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY(as stated in section D.1): ☐

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): **x**

J.3.1 Signature [13]:

J.3.2 Print name: Alan Burnett

J.3.3 Date :28/11/2012

[10] This requires a EudraLink account. (See https://eudract.ema.europa.eu/ for details)

[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.