



AML 17 Protocol Amendments: Version 7.2 June 2012 to version 8.0 October 2012

Section	Original	Change
Page 1	<p>The trial is open to all patients aged less than 60 years, <i>whether adults or children</i>, and also to patients aged 60 years or over for whom intensive therapy is considered appropriate. <i>Children are defined as patients under 16 years.</i></p> <p>In Patients who are not high risk, consolidation in adults will compare one course with two courses of High Dose Ara-C. Children will receive two courses of high dose Ara-C in consolidation.</p> <p>After course 1 of treatment, patients will be segregated based on their molecular-genetic characteristics, and a validated risk score. <i>Patients who have a FLT3 mutation will be randomised to receive the FLT3 inhibitor CEP-701 or placebo after course 1 and each subsequent chemotherapy course.</i> Patients who are at high risk of relapse based on the AML Risk Score will be eligible for an allogeneic stem cell transplant if a donor is available, <i>and/or enter a study of a novel combination.</i> These patients will be randomised between FLAG-Ida (standard arm) vs Daunorubicin/Clofarabine with the aim of maximising the number of patients receiving an allogeneic transplant. <i>Children who are high risk, will be allocated to FLAG-Ida before proceeding to transplant.</i></p> <p>Adult patients who have Core Binding Factor (CBF) leukaemias ie favourable risk disease will be randomised only to the 3 versus 4 comparison; <i>children will receive two courses of High Dose Ara-C. The rest of the adult patients will be randomised to receive, or not, mTOR inhibitor, Everolimus (RAD001) in combination with chemotherapy beginning after course 2. The Everolimus randomisation is not available for children.</i></p> <p>For <i>adult patients only</i> with APL, the Italian AIDA anthracycline plus ATRA based chemotherapy approach will be compared with the chemotherapy-free combination of ATRA plus Arsenic Trioxide. Children with APL are not eligible for AML 17.</p>	<p>The trial is open to all <i>adult</i> patients aged less than 60 years, and also to patients aged 60 years or over for whom intensive therapy is considered appropriate.</p> <p>In Patients who are not high risk, consolidation in adults will compare one course with two courses of High Dose Ara-C.</p> <p>After course 1 of treatment, patients will be segregated based on their molecular-genetic characteristics, and a validated risk score. Patients who are at high risk of relapse based on the AML Risk Score <i>and patients who have a FLT3 mutation without an NPM1c mutation irrespective of risk score</i> will be eligible for a <i>myelo-ablative or reduced intensity conditioned</i> allogeneic stem cell transplant if a donor is available. These patients will be randomised between FLAG-Ida (standard arm) vs Daunorubicin/Clofarabine with the aim of maximising the number of patients receiving an allogeneic transplant.</p> <p>Adult patients who have Core Binding Factor (CBF) leukaemias ie favourable risk disease, will be randomised only to the 3 versus 4 comparison, <i>but they will all receive gemtuzumab ozogamicin on day 1 of course 2.</i></p> <p><i>Patients who are not high risk, or favourable risk (Core Binding Factor (CBF) 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 a fully matched donor is available</i> Investigators will be informed about eligible patients..</p> <p>For patients with APL, the Italian AIDA anthracycline plus ATRA based chemotherapy approach will be compared with the chemotherapy-free combination of ATRA plus Arsenic Trioxide. Children with APL are not eligible for AML 17.</p>
Page 2	<p>Adult flow chart</p>	<p>Flow chart has been amended due to the target accrual of the FLT3+ treatment and the closure of the M-tor Randomisation. 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 ITD mutant, NPM1 WT can proceed to allogeneic transplantation (myeloablative for the ITD+/NPM1-). Recent maturing data suggests that patients who</p>

		have intermediate risk defined by the risk score who are >40 years will benefit from a Reduced Intensity allograft.
Page3	Childrens flow chart	All reference of children have been deleted from protocol, flow chart has been deleted
Page 4	Professor K Wheatley Clinical Trials Unit CRUK Institute of Cancer Studies University of Birmingham Edgbaston Birmingham B15 2TT Tel: 0121 414 3366 Fax: 0121 414 3700 e-mail: K.Wheatley@bham.ac.uk	Prof K Wheatley has been deleted from the trial Management group
Page 5	Dr Brenda Gibson (Paediatrics) Consultant Haematologist Royal Hospital for Sick Children Yorkhill Glasgow G3 8SJ Tel: 0141 201 9307 Fax: 0141 201 9303 Email: brenda.gibson@ggc.scot.nhs.uk	Dr Gibson has been deleted from the trial management group
Page 6	FLT3 INHIBITION	This has been deleted
Page 6	mTOR INHIBITION Dr Emma Das Gupta Department of Haematology Nottingham City Hospital 2nd Floor/Clinical Sciences Building Hucknall Road Nottingham NG5 1PB Tel: 0115 969 1169 ext: 54666 or bleep 7095 Fax: 0115 962 7742 Email: Emma.Dasgupta@nhs.net Professor Ken Mills Professor of Experimental Haematology CCRCB Queens University Belfast Lisburn Road Belfast, BT9 7AB Tel: 028 9097 2786 E-mail: k.mills@qub.ac.uk	Address has been deleted Ms Mandy Gilkes Department of Haematology School of Medicine Cardiff University Heath Park Cardiff CF4 14XN Tel 02920 744522 Email: gilkes@cardiff.ac.uk
Page 11 Section 2.1	To assess the value of the FLT3 inhibitor CEP-701 for patients with a FLT3 mutation To assess the value of mTOR inhibition in patients who lack a FLT3	This sentence has been deleted

	mutation, and who are not high risk, and who do not have Core Binding Factor Leukaemia	This sentence has been deleted
Page 12 Section 2.3	This section has been deleted and subsequent sections have been renumbered.	This section has been deleted and subsequent sections have been renumbered.
Page 14 Section 2.4	To correlate the blood level of anti-FLT3 activity and the extent of dephosphorylation of the FLT3 receptor with response for patients allocated to receive FLT3 inhibition therapy To assess the level of plasma mTOR activity in relation to clinical outcome.	This sentence has been deleted This sentence has been deleted
Page 15 Section 3.1	Induction phase: one randomisation to one of two arms in adults and children. Consolidation phase: for patients who are not high risk two versus one further treatment courses of high dose Ara-C (two arms)(children receive 2 courses) FLT3 inhibition for patients with FLT 3 mutations: one randomisation (two arms). mTOR inhibition for adults only (two arms)	Induction phase: one randomisation to one of two arms. Consolidation phase: for patients who are not high risk two versus one further treatment courses of high dose Ara-C (two arms) This sentence has been deleted
Page 15 Section 3.2	End of Course 1 FLT3 inhibitor (CEP-701) versus placebo, for FLT3 mutation positive patients FLAG-Ida versus D/Clofarabine for high risk score cases mTOR inhibition for non-CBF Leukaemias In poor risk patients, the role of allogeneic SCT of either Standard or Reduced intensity will be assessed by means of a genetic randomisation (i.e. donor versus no donor comparison), and by transplant given versus not given.	End of Course 1 FLAG-Ida versus D/Clofarabine for high risk score cases, and patients with a FLT3+/NPM1c ⁻ genotype. iii) The trial management system will inform investigators of whci intermediate risk patients should be considered for myeloablative or Reduced Intensity Transplant. In poor risk patients, defined by the risk score or the presence of an FLT3+/NPM1c ⁻ genotype, the role of allogeneic SCT of either Standard or Reduced intensity will be assessed by means of a Mantel Byar analysis of transplant given versus not given. Some, but not all patients with intermediate risk over 40 years of age may benefit from a reduced intensity allograft if a suitable donor is available which will also be assessed by a Mantel Byar analysis. The management system will inform investigators which patients >40 years should be considered.
Page 16 Section 3.2	By the end of the first course of induction chemotherapy (day 10), the FLT3 mutation, Should be known, allowing randomisation to the FLT3 inhibitor or not. On recovery from course 1 cytogenetics and molecular screening (Core Binding Factor) and Risk Index status of each non-APL patient will be available (the risk score is provided by the online system which must be used). Patients with a FLT3 mutation can then be randomised to start FLT3 inhibition or not for four courses after <i>each course</i> of chemotherapy (Sections 4.1.3 and 11.3). NB in children it is required that liver function tests must be within 3 X the upper limit of locally determined limit. Patients who have a high risk score will enter the comparison of Daunorubicin/Clofarabine versus FLAG-Ida (Section 11.5) Other patients who are not involved in the options (i) to (iii), will be	1. By the end of the first course of induction chemotherapy (day 20), the FLT3 and NPM1 mutation status will be reported by the reference labs, allowing the poor risk FLT3+/NPM1- patients to be identified as candidates for stem cell transplant. On recovery from course 1 cytogenetics and molecular screening (Core Binding Factor) and Risk Index status of each non-APL patient will be available (the risk score is provided by the online system which must be used). At this point patients who are candidates for a myeloablative transplant (High risk and FLT3+/NPM1c ⁻) and which standard risk patients > 40 years should be considered for a reduced Intensity Allograft from a matched sibling donore identified and indicated to the local team.

	<p>randomised to receive or not the mTOR inhibitor (Everolimus/RAD001) for 3 courses or not (Section 11.6).</p> <p>All patients except the High Risk Index patients will receive the second induction treatment course.</p>	<p>Patients who have a high risk score and FLT3+/NPM1 genotype will enter the comparison of Daunorubicin/Clofarabine versus FLAG-Ida (Section 11.3)</p> <p>Other patients who are not involved in the options (i) and (ii), will be randomised after course 2 to one or two more courses of treatment, i.e a total of three or four total courses of chemotherapy.</p> <p>All patients except the High Risk Index and FLT3+/NPM1 genotype patients will receive the second induction treatment course.</p>
Page 16	NB Consolidation for children will comprise 2 courses of High Dose Ara-C (See Section 14)	This sentence has been deleted
Page 17	<p>Patients who present with a white cell count of $>10 \times 10^9/l$ are at a slightly higher risk of relapse and should receive Mylotarg ($6mg/m^2$) to reduce the WBC in addition to the allocated treatment.</p> <p>Children with APL are not eligible for randomisation in AML17. In Children (who do not have APL or Down syndrome):</p>	<p>Patients who present with a white cell count of $>10 \times 10^9/l$ are at a slightly higher risk of relapse and should receive Mylotarg ($3mg/m^2$) to reduce the WBC in addition to the allocated treatment.</p> <p>This sentence has been deleted This sentence has been deleted</p>
Page 17	<p>At diagnosis: By the end of the first course of induction chemotherapy (day 10), the FLT3 mutation status will be available to enable randomisation to CEP-701 or placebo</p> <p>On recovery of counts Patients with a FLT3 mutation can then be randomised to start FLT3 inhibition or placebo for four courses after <i>each course</i> of chemotherapy (Sections 4.1.3 and 11.3)</p> <p>Patients with high risk disease should be treated with FLAG-Ida with a view to going to allogeneic stem cell transplant which will be assessed on a donor vs no-donor and transplant given versus not basis.</p>	<p>This sentence has been deleted</p> <p>This sentence has been deleted</p> <p>Patients with high risk disease, by score or the FLT3+/NPM1 genotype should be treated with FLAG-Ida with a view to going to allogeneic stem cell transplant which will be assessed by a Mantel-Byar analysis on a transplant given versus not basis</p>
Page 20	When we examine the role of transplantation on the new high risk group, Mantel-Byar analysis shows a significant survival advantage, although in the light of possible selection biases this result needs to be interpreted cautiously. In children, the high risk group identifies patients at a high risk of relapse. It is clear from the nearly 8000 patients entered into the MRC AML10, 12 and 15 trials that there has been no improvement in survival for high risk patients, however defined, for the last 20 years. The AML17 trial, therefore, compares a novel combination (Daunorubicin/ Clofarabine) with FLAG-Ida, in adults, with a view to proceeding to allogeneic transplantation.	When we examine the role of transplantation on the new high risk group, Mantel-Byar analysis shows a significant survival advantage, although in the light of possible selection biases this result needs to be interpreted cautiously. , In a recent review of the accumulating data from our database there is emerging evidence that, whereas to date the role of transplantation in patients with the high risk FLT3+/NPM1- genotype was uncertain, there is now evidence that this subgroup also benefit from a myeloablative stem cell transplant. The AML17 trial, therefore, compares a novel combination (Daunorubicin/ Clofarabine) with FLAG-Ida, in adults, with a view to proceeding to allogeneic transplantation.
Page 20	FLT3 Inhibition	This section has been deleted
Page 21	The new inhibitors are intended to be available to trial entrants if they relapse or are designated to be at high risk due to persistence of minimal residual disease.	This sentence has been deleted
Page 22	<p>Other Patients</p> <p>Approximately 60% of all non-APL patients have neither a FLT3 mutation nor Core Binding Factor Leukaemia. Approximately half of these adult patients (and 10% of children) will have high risk disease as defined by our new risk</p>	<p>Other Patients</p> <p>Approximately 80% of all non-APL patients do not have Core Binding Factor Leukaemia. Approximately half of these adult patients will have high risk disease as defined by our new risk score. These patients merit evaluation of novel treatment</p>

	score. These patients merit evaluation of novel treatment approaches and/or should be offered stem cell transplantation.	approaches and/or should be offered stem cell transplantation.
Page 22	<p>The cut points for designating patients as good, standard or high risk are to an extent arbitrary, and the index could be refined as new prognostic markers are incorporated eg FLT3 status. FLT3 has been excluded from the score to be used in AML17 because such patients are being assessed in the FLT3 inhibitor part of AML17.</p> <p>For the purposes of the AML17 trial patients who have a risk score of greater than 2.667, who do not have a FLT3 mutation or Core Binding Factor Leukaemia will be designated as high risk with a predicted survival at 5 years of 24% (based on AML10, 12).</p> <p>It is uncommon for children to be high risk as defined by the risk score. However such children will be allocated to FLAG-Ida treatment with a view to proceeding to allogeneic stem cell transplant if a donor is identified.</p>	<p>The cut points for designating patients as good, standard or high risk are to an extent arbitrary, and the index could be refined as new prognostic markers are incorporated e g FLT3 status. FLT3 has been excluded from the score to be used in AML17 but it is now recognised that non-high risk patients with an FLT3+/NPM1- genotype may also benefit from stem cell transplant..</p> <p>For the purposes of the AML17 trial patients who have a risk score of greater than 2.667 or the FLT3+/NPM1 genotype will be designated as high risk with a predicted survival at 5 years of 24% (based on AML10, 12).</p> <p>This sentence has been deleted</p>
Page 22	m TOR Inhibition	This section has been deleted
Page 30	Dr P White	Ms M Gilkes

Page 33	The physician and patient consider that intensive therapy is not an appropriate treatment option. (Such patients should be considered for the NCRI AML16 trial for older or less fit patients). CHILDREN WITH APL AND DOWN SYNDROME AND AML ARE NOT ELIGIBLE FOR AML 17	The physician and patient consider that intensive therapy is not an appropriate treatment option. (Such patients should be considered for current NCRI trial for older or less fit patients). This sentence has been deleted
Page 33 section 8.1.1	The relevant information and consents 1A should be used for children.	This sentence has been deleted
Page 33 Section 8.2.1	For children use forms 2A.	This sentence has been deleted
Page 34 Section 8.2.1	Patients including children have a 50% chance of receiving each of the treatments. For children under 10 use the Play Performance Scale (see Appendix F)	Patients have a 50% chance of receiving each of the treatments. This sentence has been deleted
Page 34 Section 8.3.1	Professor Harrison will coordinate cytogenetics in children.	This sentence has been deleted
Page 34 Section 8.3.2	8.3.2 FLT3 Mutation Status and Molecular Screening Investigators will be informed of the FLT3 mutation status of patients to determine eligibility for the FLT3 inhibition randomisation. It is essential that a sample is sent to a designated laboratory for the identification of patients with a FLT3 mutation. These laboratories will pass samples on to the laboratories designated for MRD monitoring. It is intended that investigators will have the results of FLT3 assays by the end of the first course of chemotherapy to enable eligible patients to be randomised between FLT3 inhibitor or placebo. For children 2 ml of bone marrow and 8 and 8ml of blood in EDTA (2ml for infants)	8.3.2 FLT3/NPM1c Mutation Status and Molecular Screening Investigators will be informed of the FLT3/NPM1c mutation status of patients It is essential that a sample is sent to a designated laboratory for the identification of patients with a FLT3/NPM1c mutations. These laboratories will pass samples on to the laboratories designated for MRD monitoring. It is intended that investigators will have the results of FLT3 assays within approximately two weeks of the end of the first course of chemotherapy. This sentence has been deleted
Page 40	Mr Steve Couzens Department of Haematology University Hospital of Wales Heath Park, Cardiff CF14 4XN Tel: 029 20742370 Fax : 029 20745084 e-mail: Couzenssj@cardiff.ac.uk	Dr Paul White Department of Haematology University Hospital of Wales Heath Park, Cardiff CF14 4XN Tel: 029 20742370 Fax : 029 20745084 e-mail: whitepc@cardiff.ac.uk
Page 37 Section 8.4	Molecular Inhibition (Form D) - return for patients allocated to receive either FLT3 or mTOR inhibitor	This sentence has been deleted
Page 37 Section 8.4	For patients allocated to FLT3 or mTOR inhibition will be sent periodic forms to assess compliance and toxicity. Adverse event forms can be downloaded from the website. Investigators will be able to report event via the website, but should retain a hard copy in the Study Site file and the patients' notes.	This sentence has been deleted
Page 37 Section 9	After Course 1, the additional or alternative treatments will be decided as patients are characterised as having Core Binding Factor leukaemia, the presence of a FLT3 mutation, a high risk score, or none of these.	. After Course 1, the additional or alternative treatments will be decided as patients are characterised as having Core Binding Factor leukaemia, a high risk score, a FLT3/NPM1c genotype or none of these.

Page 38 Section 9.2	<p>All drug doses should be reduced by 25% in children aged less than one year or weighing less than 10kgs.</p> <p>Seven to 10 days before commencement of course 2, patients should have a tropoinin level and an ejection fraction done, to monitor for subclinical cardiac effects.</p>	<p>This sentence has been deleted</p> <p>Seven to 10 days before commencement of course 2, patients should have a tropoinin level and an ejection fraction done, to monitor for subclinical cardiac effects. It is intended that Investigators will be offered access to a more detailed companion project monitoring the cardiac function of patients in the Daunorubicin randomisation. This will be co-ordinated by Dr Ann Hunter.</p>
Page 39 Section 10	<p>In addition a paired marrow and blood sample should be sent to the relevant reference immunophenotyping laboratory and a separate paired sample to Prof Yin (for CBF leukaemias) or Prof Grimwade (other molecular targets) for molecular assessment of MRD (see Sections 8.3.4, 11.4 and 20.10 for addresses). Rarely patients with a FLT3 mutation will emerge as also having favourable cytogenetics. Such patients should continue on the FLT3 inhibitor allocated therapy. Favourable risk patients should also be randomised to receive 3mg/m² of Mylotarg if they have not received it in course 1</p>	<p>In addition a paired marrow and blood sample should be sent to the relevant reference immunophenotyping laboratory and a separate paired sample to Prof Grimwade for molecular assessment of MRD (see Sections 8.3.3, 11.2 and 19.10 for addresses). Favourable risk patients should also be randomised to receive 3mg/m² of Mylotarg ion day 1 of course 2.</p>
Page 39 Section 11	<p>ADDITIONAL TREATMENTS</p> <p>11.1 Additional treatments</p> <p>Immediately after the completion of chemotherapy patients become eligible for additional or alternative treatment. Within 10 days of entering the trial the reference labs will have defined the FLT3 mutation status. If a mutation is found the site Principal Investigator (PI) and research nurses will be informed thus enabling the patient to enter the FLT3 Inhibitor randomisation (Section 11.3). After recovery of blood counts and marrow assessment of response additional information will be available. Patients with Core Binding Factor Leukaemias will be identified and sufficient information will be available to calculate the individual patient's risk score. The investigator should ascertain the risk score which is calculated and provided by the internet data system which will inform investigators if the patient has a high risk score or not , and what treatment options the patient is eligible for. (for high risk see Section 11.5). Patients who are in none of these categories are eligible for the addition of mTOR inhibition (Section 11.6), which will start after course 2. The computer randomisation system will identify which randomisation patients are eligible to enter (by calculating risk score and identifying patients who are either CBF or have a FLT3 mutation).</p> <p>Patients in these randomisations will be randomised in a 2:1 fashion, so that there is a two out of three chance of receiving either mTOR or FLT3 inhibitor or Daunorubicin/Clofarabine in the high risk option. The FLT3 patients will receive active drug or placebo.</p> <p>Some patients will be considered to be primarily refractory if the marrow blast count has not been reduced by >50% with course 1. These patients can enter the high risk option irrespective of other score parameters.</p>	<p>SUBSEQUENT TREATMENTS</p> <p>11.1 Subsequent Treatments</p> <p>After recovery of blood counts and marrow assessment of response additional information will be available. Patients with Core Binding Factor Leukaemias will be identified and sufficient information will be available to calculate the individual patient's risk score. The investigator should ascertain the risk score which is only calculated and provided by the internet data system which will inform investigators if the patient has a high risk score or not , and what treatment options the patient is eligible for. (for high risk see Section 11.3. The computer randomisation system will identify which randomisation patients are eligible to enter (by calculating risk score and identifying patients who are either CBF or have a FLT3+/NPM1c genotype).</p> <p>Patients in the high risk group will be randomised in a 2:1 fashion, so that there is a two out of three chance of receiving Daunorubicin/Clofarabine in the high risk option.</p> <p>Some patients will be considered to be primarily refractory if the marrow blast count has not been reduced by >50% with course 1. These patients can enter the high risk option irrespective of other score parameters.</p> <ul style="list-style-type: none"> - For patients eligible for the high risk treatments use Patient Information Sheet 5 and Consent Form 5

Page 40	<p>11.2 Patient Information and Consent</p> <p>11.3 FLT3 INHIBITION</p> <p>11.3.1 CEP-701 TREATMENT</p> <p>11.3.2 Dose Adjustment</p> <p>11.3.3 CEP701 Day 14 assessment visit</p>	<p>This section has been deleted</p> <p>These sections has been deleted</p>
Page 42 Section 11.4	<p>11.4 CORE BINDING FACTOR LEUKAEMIA</p> <p>This information can be provided on a commercial basis by arrangement with the Manchester lab contact details below:</p> <p>Prof J A L Yin Department of Haematology Manchester Royal Infirmary Oxford Road Manchester M13 9WL Tel: 0161 276 4802 (direct to Sec) Fax: 0161 276 4814 Email: jyin@labmed.cmht.nwest.nhs.uk</p> <p>It is recognised that a small number of Core Binding Factor Leukaemias will already have entered the FLT3 inhibitor randomisation before the cytogenetic information was available. These patients should continue in the FLT3 assessment and should continue to receive the inhibitor medication. to It is possible (but unlikely) that the cytogenetic definition of CBF leukaemia may become available before the FLT3 mutation status. These patients should enter the FLT3 randomisation.</p>	<p>11.2 CORE BINDING FACTOR LEUKAEMIA</p> <p>This section has been deleted</p>
Page 42 section 11.3	<p>11.5 HIGH RISK SCORE PATIENTS</p> <p>The cytogenetic result will be automatically entered by the relevant cytogenetic lab, but the investigator is responsible for entering the marrow response to course 1.The internet system will allocate the risk category and indicate what treatment options are available.</p>	<p>11.3 HIGH RISK SCORE PATIENTS.</p> <p>The cytogenetic result will be automatically entered by the relevant cytogenetic lab, but the investigator is responsible for entering the marrow response to course 1.The molecular screening labs in Cardiff and UCH will automatically inform the database of the FLT3/NPM1c mutation genotype and the system will inform the site if they should be managed as high risk. The internet system will allocate the risk category and indicate what treatment options are available.</p>
Page 44	<p>Children who are assessed to be high risk will enter the FLAG-Ida arm only.</p>	<p>This sections has been deleted</p>
Page 46 section 11.6	<p>11.6 mTOR Inhibition - Everolimus</p> <p>11.6.1 Dose Adjustment</p> <p>11.6.2 Everolimus Day 14 assessment visit</p>	<p>These sections has been deleted</p>
Page 46 Section 11.6	<p>FLT3 mutation status should be available by the end of the first course of chemotherapy, (see Section 10). After recovery from course 1 and assessment of response, the risk score can be provided for individual</p>	<p>FLT3/NPM1c mutation status should be available by the end of the first course of chemotherapy. After recovery from course 1 and assessment of response, the risk score can be provided for individual patients who do not have Core Binding Factor</p>

	<p>patients who are not already in the CEP-701 randomisation or with Core Binding Factor Leukaemia. Patients who have been allocated to receive an inhibitor should continue to receive the inhibitor irrespective of which consolidation chemotherapy arm is allocated</p>	<p>Leukaemia</p> <p>This sentence has been deleted</p>
Page 47 Section 12	Note: the consolidation options for children (patients < 16 years of age) is different and is set out in Section 13.2	This sentence has been deleted
Page 47 Section 12.1	Patients who have already been allocated to receive FLT3 or mTOR inhibition will continue with that treatment as well.	This sentence has been deleted
Page 48 section 12.3	Whether already enrolled in the FLT3 or mTOR inhibitor randomisations	This sentence has been deleted
Page 48 section 13	Patients who have entered the FLT3 inhibitor or mTOR randomisation, and who have been allocated CEP-701 or Everolimus respectively, should receive the drug after courses 3 and 4 as described in sections 11.3 and 11.6.	This section has been deleted
	13.2 Consolidation for Children	This section has been deleted
Page 49 Section 14	<p>14 SUMMARY OF MODIFICATIONS FOR CHILDREN</p> <p>14.1 Eligibility</p> <p>14.2 Treatment Variations for Children</p> <p>14.3 Paediatric Management Group</p> <p>14.4 Central Nervous System Prophylaxis and Treatment in Children</p> <p>14.4.1 No CNS disease</p> <p>14.4.2 CNS disease at diagnosis</p> <p>14.5 Stem Cell Transplant</p> <p>14.5.1 Dosing guidance</p> <p>14.5.2 Summary of chemotherapy reductions for children under one year of age or less than 10kg</p> <p>14.6 CEP701</p>	These sections have been deleted
Page 52 Section 14	<p>15 STEM CELL TRANSPLANTATION</p> <p>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.</p> <ol style="list-style-type: none"> 1. Patients <35 years should receive a conventional allogeneic transplant with Cyclophosphamide and Total Body Irradiation (8 x 180cGy fractions). [For children aged less than 2 year, conditioning should be with Busilphan and Cyclophamide 2. Patients 35-44 years can receive a conventional allogeneic transplant or a reduced intensity allograft (RIC) depending on investigator or patient choice. 3. Patients ≥45 years should receive a Reduced Intensity allograft (RIC)."mini" allograft 	<p>14 STEM CELL TRANSPLANTATION</p> <p>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+/NPM1c- genotype. Recent maturing data suggests that some 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. The management system will inform investigators at the time of risk assessment which older standard risk patients should be considered. As soon as a potential donor is identified the transplant centre should be informed. The transplant should be carried out 6-8 weeks after the final course of chemotherapy. The type of transplant and the transplant protocol will be determined by the transplant centre's usual policy. As a guide based on prior evidence:</p> <ol style="list-style-type: none"> 1. Patients <35 years should receive a conventional allogeneic transplant with Cyclophosphamide and Total Body Irradiation (8 x 180cGy fractions).

15.1 Conventional Allogeneic Transplantation

If the patient meets the criteria of the transplant centre, he/she will receive the transplant as soon as is practical. It is expected that they will have received one or two of the allocated treatment courses in the high risk arm. The most widely used myeloablative schedule is Cyclophosphamide and Total Body Irradiation (8 x 180 cGy). The source of stem cells can be bone marrow or peripheral blood. If peripheral blood is used, a dose of at least 4 x 10⁶ CD34 cells/kg should be given. Graft versus host prophylaxis will be determined by the transplant centre, but the most widely used is Methotrexate and Cyclosporin. It is required that patients who receive a transplant will provide written consent in line with the transplant centre policy. Children intended for SCT will have a conventional allograft following CCLG Protocols (Section 14).

15.2 Reduced Intensity Allograft

Patients who will receive a reduced intensity allograft must first receive two courses of the high risk arm and the **mini-allograft as Course 4**. The mini-allograft should only be carried out at centres with experience of this approach and should **not be carried out in centres who do not perform conventional allografts**. The precise protocol to be used in the AML17 trial will be that chosen by the transplant centre, but may be subject to change in light of emerging evidence in the field.

Transplant centres initially may wish to choose one of two reduced intensity protocols:

FBC Protocol:

Fludarabine	30 mg/m ² /day	days
-9 to -5 inclusive		
Busulphan	4 mg/kg/day	days
-3 and -2		
Campath 1H	20 mg/day i.v.	days
-5 to -1 inclusive		

(use of phenytoin and low molecular weight heparin for VOD prophylaxis is optional)

Fludara, Melphalan, Campath (UCL) Protocol:

Fludarabine	30 mg/m ² /day	days
-7 to -3 inclusive		
Melphalan	140 mg/m ²	on day -2
Campath 1H	20 mg/day	days
-8 to -4 inclusive		

Since patient and donor will require time to be counselled about the transplant option which may be delivered as early as course 3, investigators are encouraged to identify donor availability as soon as possible after

2. Patients 35-40 years can receive a conventional allogeneic transplant or a reduced intensity allograft (RIC) depending on investigator or patient choice
3. Patients ≥40 years should receive a Reduced Intensity allograft (RIC)..

14.1 Conventional Myelo-Ablative Allogeneic Transplantation

If the patient meets the criteria of the transplant centre, he/she will receive the transplant as soon as is practical. It is expected that they will have received one or two of the allocated treatment courses in the high risk arm. The most widely used myeloablative schedule is Cyclophosphamide and Total Body Irradiation (8 x 180 cGy). The source of stem cells can be bone marrow or peripheral blood. If peripheral blood is used, a dose of at least 4 x 10⁶ CD34 cells/kg should be given. Graft versus host prophylaxis will be determined by the transplant centre, but the most widely used is Methotrexate and Cyclosporin. It is required that patients who receive a transplant will provide written consent in line with the transplant centre policy

14.2 Reduced Intensity Allograft Schedules

Patients who will receive a reduced intensity allograft must first receive two courses of the high risk arm and the mini-allograft as Course 4. The mini-allograft should only be carried out at centres with experience of this approach and should not be carried out in centres who do not perform conventional allografts. The precise protocol to be used in the AML17 trial will be that chosen by the transplant centre, but may be subject to change in light of emerging evidence in the field. For patients with intermediate risk cytogenetics either the FMC or FBC protocol (see below) is recommended. Emerging evidence suggests that patients with poor risk disease may benefit from a more intensive conditioning regimen and the "FLAMSA-Bu" schedule should be considered (see below). Supervision of this schedule is being undertaken by Prof C Craddock (page 5 for contact details) who should be informed of each patient who is planned for this approach to RIC transplant.

14.2.1 Reduced Intensity Protocols for Patients with Intermediate Risk Disease

4. FBC Protocol:

Fludarabine	30 mg/m ² /day	days
-9 to -5 inclusive		
Busulphan	4 mg/kg/day	days
-3 and -2		
Campath 1H	20 mg/day i.v.	days
-5 to -1 inclusive		

(use of phenytoin and low molecular weight heparin for VOD prophylaxis is optional)

5. Fludara, Melphalan, Campath (UCL) Protocol:

Fludarabine	30 mg/m ² /day	days
-7 to -3 inclusive		
Melphalan	140 mg/m ²	on day -2

diagnosis. Collection of Autologous stem cells is not an inherent part of the AML17 trial but nor is it proscribed. On completion of the transplant the "Transplant" form (Form E) should be completed via the web-based system.

Campath 1H 20 mg/day days -8 to -4
inclusive

14.2.3 FLAMSA-Bu Schedule for Patients 60 years old with High Risk Disease and under who are fit for transplant:

Eligible patients 60 years or younger with high risk disease and an available matched sibling or 8/8 or 7/8 adult volunteer unrelated donor will undergo transplantation utilising the following regimen:

- Day -12 to -9: Intravenous chemotherapy
- Day -12 to -9: Fludarabine 30 mg/m²/d
- Day -12 to -9: Cytarabine 2 g/m²/d
- Day -12 to -9: Amsacrine 100 mg/m²/d
- Day -8 to -6: Rest day
- Day -5 to -2: Conditioning :
 - IV Busulphan, total dose 11.2 mg/kg
 - IV Fludarabine, total dose 60 mg/m²
- Day -5: IV Bu3.2 mg/kg/day once-daily over 3 hours
- Day -4: IV Bu.....3.2 mg/kg/day once-daily over 3 hours
- Day -3: IV Bu..... 3.2 mg/kg/day once-daily over 3 hours
- Day -2: IV Bu1.6 mg/kg/d for once-daily over 3 hours
- Day -3 to -2: Flu 30 mg/m²/day once daily IV over 1 hour

ATG (Fresenius) on day -3, -2 and -1,
(dose adapted to the donor type. Total dose 10 mg/kg for patients with a sibling donor or Total dose 20 mg/kg for patients with unrelated donors)

- Day -1: Initiation of GVH disease prophylaxis with Cyclosporin
- Day 0: Initiation of GVH disease prophylaxis with MMF
- Day 0: Infusion of sibling or unrelated donor PBSCT or BMT

14.2.4 Patients over 60 years old with High Risk Disease who are fit for transplant:
Eligible patients over 60 years of age with high risk disease with an available matched sibling or 8/8 or 7/8 adult volunteer unrelated donor will undergo transplantation utilising the following regimen:

- Day -12 to -9: Intravenous chemotherapy
- Day -12 to -9: Fludarabine 30 mg/m²/d
- Day -12 to -9: Cytarabine 2 g/m²/d
- Day -12 to -9: Amsacrine 100 mg/m²/d
- Day -8 to -5: Rest day
- Day -4 to -2: Conditioning :
 - IV Busulphan total doses 8 mg/kg
 - IV Fludarabine total dose 60 mg/m²
- Day -4: IV Bu at 3.2 mg/kg/d in 3 hours
- Day -3: IV Bu at 3.2 mg/kg/ in 3 hours

		<p>Day -2: IV Bu at 1.6 mg/kg/d in 3 hours Day -3 to -2: IV Flu 30 mg/m²/d once daily over 1 hour ATG (Fresenius) on day -3, -2 and -1, (dose adapted to the donor type. Total dose 10 mg/kg for patients with a sibling donor or Total dose 20 mg/kg for patients with unrelated donors)</p> <p>Day -1: Initiation of GVH disease prophylaxis with Cyclosporin Day 0: Initiation of GVH disease prophylaxis with MMF Day 0: Infusion of sibling or unrelated donor PBSCT or BMT</p> <p>Donor lymphocyte infusions (DLI) to be administered at day +120 post transplant in patients in remission if there is no history of GVHD and immunosuppression has been discontinued. Up to three transfusions will be scheduled using an escalating dose regimen until 100 donor T cell chimerism is achieved. Patients with a related donor will receive an incremental dose schedule of 1 x 10⁶, 5 x 10⁶ and 1 x 10⁷ CD3+ cells/kg administered every 2 months. Patients with an unrelated donor will receive an escalating schedule of 5 x 10⁵, 1 x 10⁶ and 5 x 10⁶ CD3+ cells/kg.</p> <p>Since patient and donor will require time to be counselled about the transplant option which may be delivered as early as course 3, investigators are encouraged to identify donor availability as soon as possible after diagnosis. Collection of Autologous stem cells is not an inherent part of the AML17 trial but nor is it proscribed. On completion of the transplant the "Transplant" form (Form D) should be completed via the web-based system.</p>
Page 53 Section 15.1	These labs will undertake the FLT3 mutation assessment to enable entry into the FLT3 inhibitor randomisation. Samples will also be assessed for in vitro sensitivity to CEP-701.	These labs will undertake the FLT3/NPM1c mutation assessment.
Page 53 Section 15.2	<p>AML1-ETO/CBFB-MYH11</p> <p>Dr Abida Awan/Prof Yin Molecular Diagnostics Centre Top Floor, Multi-purpose Building Manchester Royal Infirmary Oxford Road Manchester M13 9WL Tel: 0161 276 4137 Fax: 0161 276 4814 Email: abida.Awan @cmmc.nhs.uk</p> <p>Samples from children for molecular screening and MRD monitoring should be sent to their designated reference laboratory (Paul Virgo, Bristol)</p>	<p>This has been deleted</p> <p>This has been deleted</p>
Page 55 Section 15.4	Mr Steve Couzens Department of Haematology University Hospital of Wales Heath Park, Cardiff	Dr Paul White Department of Haematology University Hospital of Wales Heath Park, Cardiff

	CF14 4XN Tel: 029 2074 2370 Fax : 029 2074 5084 e-mail: Couzenssj@cardiff.ac.uk	CF14 4XN Tel: 029 2074 2370 Fax : 029 2074 5084 e-mail: whitepc@cardiff.ac.uk
Page 57	The approach to CNS prophylaxis is different for children and is described Section 14.3.	This sentence has been deleted
Page 64 Section 20.1	For the randomisations to targeted therapy, approximately 90% of patients (i.e. 2450 patients) will commence their second course of treatment. Data from previous MRC AML trials have been used to determine the likely recruitment to each question. It is anticipated that at least 300 patients will enter the CEP-701 randomisation where two thirds of the patients will receive CEP-701. Together with the approximately 200 patients who will be randomised (in a 1:1 fashion) as part of AML15, this gives a total of at least 500 patients in this comparison. . Data from the AML10,12 trials show that five-year DFS in this group is about 33%; so the meta-analysis of AML15 and AML17 should have 80% power to detect a difference in DFS of 12% (from 33% to 45%).	This paragraph has been deleted
Page 63	<p>Assuming that around 15% of non-APL patients will have a core binding factor leukaemia, there remains a group of approximately 900 patients who do not fall into one of the predefined categories (CBF, FLT-3 positive, poor risk), and are therefore eligible for randomisation between mTOR inhibition and not. Assuming a 70% uptake of this randomisation, this means that there should be in excess of 600 patients who will be randomised in a 2:1 ratio between mTOR inhibitor and not. With 600 patients recruited there will be 85% power to detect a 12.5% improvement in disease-free survival (from 50% to 62.5% at 5 years). Again a primary endpoint of DFS is chosen because of the option for patients who relapse to enter the “poor risk” randomisation.</p> <p>Of the patients who are not considered to be “poor risk”, at least 80% should enter CR and therefore eligible for the consolidation randomisations. This equates to around 1600 patients. Even if only two-thirds of such patients are randomised to the consolidation questions (roughly equivalent to the rate in AML15), there will be at least 1000 patients for the 3v4 course randomisation. This will be powered as a non-inferiority trial with a one-sided significance level of p=0.025. With 90% power there will be sufficient power to detect or rule out inferiority in 5 year survival from CR (the primary endpoint) of 65% versus 55%.</p> <p>To investigate the effect of MRD monitoring, the project will run in several stages. Initially, the best cut-offs will be identified; because a number of different time-points will be investigated, all analyses will be performed at a</p>	<p>Just under 30% of patients starting their second course will be poor risk (i.e. approximately 700 patients). In the first instance, patients will be randomised between DClo v FLAG-Ida in a 2:1 randomisation. In the first half of the trial, therefore, one might expect a recruitment of around 300 patients. Five-year survival of this group of patients is currently 30%, so recruiting 315 patients in the first half of the trial will give 80% power to detect a clinically meaningful 15% improvement in survival from 30% to 45%. If the randomisation ran for the entirety of the trial, recruiting approximately 480 patients, then there would be 90% power to detect a 15% difference in 3-year survival difference from 40% to 55% with 234 deaths. Should other new therapies suitable for this group of patients become available during the course of the trial these can then be introduced by protocol modification. At present only around 40% of poor risk patients entering CR receive a transplant; with 360 patients randomised there will be approximately 80% power to detect an improvement from 40% to 55% in the numbers being transplanted, and 90% power to detect the same improvement with 480 patients.</p> <p>Of the patients who are not considered to be “poor risk”, at least 80% should enter CR and therefore be eligible for the 3 vs 4 course randomisation. This equates to around 1600 patients. Even if only two-thirds of such patients are randomised, there will be 1000 patients for the 3v4 course randomisation. This will be powered as a non-inferiority trial with a one-sided significance level of p=0.025. With 90% power there will be sufficient power to detect or rule out inferiority in 5 year survival from CR (the primary endpoint) of 65% versus 55%.</p> <p>To investigate the effect of MRD monitoring, the project will run in several stages. Initially, the best cut-offs will be identified; because a number of different time-points will be investigated, all analyses will be performed at a 1% significance level. Around</p>

	<p>1% significance level. Around 80% of patients enter CR, and it is anticipated that about 50% of these will achieve MRD negativity. Approximately half of all patients will relapse in the first 3 years. With a total of 360 patients entering CR (i.e. 450 patients with suitable markers), there will be 90% power to detect a difference between groups of 20% (40% versus 60% relapsing). Thus, it is planned that the first stage of the process will run for the first 600 patients, to allow for 20% of patients not having suitable markers. At this point the future direction of the MRD project will be assessed based on the preliminary results, and the treatment randomisation powered in line with the results found in the first stage.</p>	<p>80% of patients enter CR, and it is anticipated that about 50% of these will achieve MRD negativity. Approximately half of all patients will relapse in the first 3 years. With a total of 360 patients entering CR (i.e. 450 patients with suitable markers), there will be 90% power to detect a difference between groups of 20% (40% versus 60% relapsing). Thus, it is planned that the first stage of the process will run for the first 600 patients, to allow for 20% of patients not having suitable markers.</p> <p>Sequential monitoring has proved feasible in about 50% of patients; and these patients have 5 year survival of approximately 55%. There should be approximately 600 patients eligible to be randomised during the course of the trial in a 2:1 ratio (monitor vs no monitor). This is sufficient with 80% power to detect an increase from 55% survival to 67%, with 198 deaths overall.</p>
Page 64	<p>The main analyses will be based on the intention to treat - i.e. all patients believed to be eligible at the time of randomisation will be included in the analysis, irrespective of protocol compliance, early death, etc. Comparisons of randomised treatments will be made using the log-rank test for time to event outcomes; and the Mantel-Haenszel test for dichotomous outcomes. Resource usage data will be compared using Wilcoxon rank-sum tests or t-tests as appropriate. The primary outcome is survival for all randomisations except the APL randomisation (see below),</p>	<p>The main analyses will be based on the intention to treat - i.e. all patients believed to be eligible at the time of randomisation will be included in the analysis, irrespective of protocol compliance, early death, etc. Comparisons of randomised treatments will be made using the log-rank test for time to event outcomes; and the Mantel-Haenszel test for dichotomous outcomes. Resource usage data will be compared using Wilcoxon rank-sum tests or t-tests as appropriate. The primary outcome is survival for all randomisations except the APL randomisation (see below),</p>
Page 62 Section 22.1	<ul style="list-style-type: none"> - Development of a non-haematological toxicity of grade 3 as defined in the NCI Common Toxicity Criteria**, which does not resolve to grade 2 or less within 7 days - Development of any grade 4 non-haematological toxicity (excluding alopecia) - Development of neutropenia (<1.0 x 10⁹/L) or thrombocytopenia (<50 x 10⁹/L) for longer than 42 days after the end of chemotherapy in the absence of significant disease in the bone marrow (>5% blasts) - Any event which results in persistent or significant disability or incapacity - Any event which results in a congenital abnormality or birth defect - Death from any cause including persistent or progressive disease 	<ul style="list-style-type: none"> - Development of a non-haematological toxicity of grade 3 as defined in the NCI Common Toxicity Criteria Version 3**, which does not resolve to grade 2 or less within 7 days - Development of any grade 4 non-haematological toxicity (excluding alopecia) (this includes any life threatening event) - Development of neutropenia (<1.0 x 10⁹/L) or thrombocytopenia (<50 x 10⁹/L) for longer than 42 days after the end of chemotherapy in the absence of significant disease in the bone marrow (>5% blasts) - Events which are not related to AML or its treatment which result in hospitalisation or prolongation of hospitalisation. - Any event which results in persistent or significant disability or incapacity - Any event which results in a congenital abnormality or birth defect - Death from any cause including persistent or progressive disease - Other Medically important event*

Page 63 section 22.1.5	<p>Unblinding SUSAR's in patients randomised to the CEP 701/Placebo trial arm.</p> <p>All sites will be provided with Code break envelopes once their patient has been randomised to the CEP 701/Placebo arm of the trial. These are normally held by the site pharmacy department.</p> <p>The CEP701/Placebo arm of the study should only be unblinded for a valid medical or safety reason, for example, a serious adverse where it is necessary for the PI or treating healthcare professional to know which treatment the patients has been receiving to ensure the participant can receive appropriate safety measures. In this event the research team should contact the Trials office at 029 2184 7928 (office hours) or 029 20747747 (outside office hours, this is the hospital switchboard telephone number who has a direct number for the CI or his delegate).</p>	
Page 73 – Appendix B	<p>Etoposide</p> <p>CEP-701 (Cephalon Inc.)</p> <p>RAD001 (Everolimus Novartis)</p>	These drugs in this section have been deleted.
Page 77	<p>APPENDIX C Background Information on CEP-701</p> <p>APPENDIX D Instructions to the Patient/Caregiver for Administering CEP-701 25mg/ml/Placebo oral solution.</p>	Appendix C and D deleted therefore subsequent appendices have been re-lettered
Page 85	APPENDIX F WHO Play Performance Scale For Children Aged 0-9 Years	Appendix F deleted therefore subsequent appendices have been re-lettered