

# An international randomised clinical trial of therapeutic interventions with the potential to improve outcome in adults with acute myeloid leukaemia and high-risk myelodysplasia undergoing allogeneic stem cell transplantation

<b>Submission date</b> 18/03/2019	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 20/03/2019	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 10/09/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-usual-treatment-new-treatments-acute-myeloid-leukaemia-myelodysplasia-cosi>

## Contact information

### Type(s)

Scientific

### Contact name

Dr Cosi trials

### Contact details

Haematology Team – IMPACT  
Room 15  
Centre for Clinical Haematology  
Queen Elizabeth Hospital  
Edgbaston  
Birmingham  
United Kingdom  
B15 2TH  
+44 (0)121 371 7859  
Cosi@trials.bham.ac.uk

## Additional identifiers

## Clinical Trials Information System (CTIS)

2017-004801-42

## Integrated Research Application System (IRAS)

252254

## ClinicalTrials.gov (NCT)

NCT04217278

## Protocol serial number

CPMS 41409, IRAS 252254

# Study information

## Scientific Title

An international randomised clinical trial of therapeutic interventions with the potential to improve outcome in adults with acute myeloid leukaemia and high-risk myelodysplasia undergoing allogeneic stem cell transplantation

## Acronym

COSI

## Study objectives

The aim of the study is to evaluate new pre-transplant and transplant strategies to improve the outcome of patients allografted for AML or high-risk MDS.

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Approved 16/05/2019, North West - Liverpool Central Research Ethics Committee, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, Tel: +44 (0)207 104 8196, Email: liverpoolcentral.rec@hra.nhs.uk, ref: 19/NW/0135

## Study design

Randomised; Interventional; Design type: Treatment, Drug

## Primary study design

Interventional

## Study type(s)

Treatment

## Health condition(s) or problem(s) studied

Acute myeloid leukaemia, myelodysplastic syndromes

## Interventions

There are three separate randomisations in this trial.

Randomisation 1 (R1) - patients will be randomised 1:1 to either the experimental arm (Vyxeos pre-transplant consolidation therapy) or the control arm (Intermediate dose cytarabine pre-transplant consolidation therapy). In the control arm patients will receive up to 2 cycles of cytarabine administered as a 2-hour infusion at a dose of 1 g/m<sup>2</sup> on days 1-5 of each cycle. In the experimental arm patients will receive up to 2 cycles of Vyxeos administered intravenously over 90 minutes at a dose of 29 mg/65mg/m<sup>2</sup> on days 1 and 3 of each cycle.

Randomisation 2 (R2) - patients aged under 55 years will be randomised 1:1 to either the experimental arm (novel myeloablative conditioning regimen TBF) or the control arm (standard myeloablative conditioning regimen FB4). Patients will receive the allocated myeloablative conditioning regimen in hospital immediately prior to allogeneic stem cell transplant.

Randomisation 3 (R3) - patients aged 55 years and over will be randomised 1:1:1 to either one of the two experimental arms (novel reduced intensity conditioning regimen mini TBF or mini FLAMSA-BU) or the control arm (standard reduced intensity conditioning regimen FB2). Patients will receive the allocated reduced-intensity conditioning regimen in hospital immediately prior to allogeneic stem cell transplant.

Patients can be randomised to just one of the above randomisations, or can be randomised twice (e.g. R1 and R2 or R1 and R3). All patients will be followed up for 2 years.

### **Intervention Type**

Drug

### **Phase**

Phase II/III

### **Drug/device/biological/vaccine name(s)**

Liposomal cytarabine-daunorubicin (Vyxeos), cytarabine, fludarabine, busulphan, thiotepa

### **Primary outcome(s)**

Current primary outcome measure as of 09/12/2022:

Overall survival defined as the time from randomisation to the relevant question until death from any cause. Patients who are alive at the end of the trial or have been lost to follow-up will be censored at their date last seen. For randomisations 2 and 3 this outcome will also be calculated as time from transplantation in order to run a sensitivity analysis.

Previous primary outcome measure:

Overall survival defined as the time from randomisation to death from any cause. Patients who are alive at the end of the trial or have been lost to follow up will be censored at their date last seen. For randomisations 2 and 3 this outcome will also be calculated as time from transplantation in order to run a sensitivity analysis.

### **Key secondary outcome(s)**

Current secondary outcome measure as of 09/12/2022:

1. Measurable residual disease (MRD) status, collected on randomisation and then again immediately prior to transplant. A patient will be categorised as either MRD status reduction (MRD positive to negative), MRD remain negative, MRD remain positive or MRD progression (MRD negative to positive) – Randomisation 1 only (closed to recruitment).
2. Disease-free survival defined as time from randomisation to the relevant question to the date

of first relapse or death from any cause. Patients who are alive and disease free at the end of the trial will be censored at their date last known to be alive.

3. Cumulative incidence of disease relapse defined as time from randomisation to the relevant question to the date of relapse. Patients who die prior to relapse will be treated as a competing risk and patients who are alive and relapse free at the end of the trial will be censored at their date last seen

4. Non-relapse mortality defined as the time from randomisation to date of non-relapse death. Patients who die post-relapse will be treated as a competing risk and patients who are alive at the end of the trial will be censored at their date last seen

5. Quality of life measured by EORTC-QLQ-C30 and EQ-5D questionnaires pre transplant, at day 28 and months 3, 6, 9, 12, 18 and 24 – Randomisations 2 and 3 only

6. Incidence of acute and chronic GVHD of any grade – Randomisations 2 and 3 only

7. Incidence of primary graft failure – Randomisations 2 and 3 only

8. Incidence of toxicities reported as per CTCAE V4.0 defined as the number of patients who report one or more AE of grade 3 or higher or an SAE of any grade

Previous secondary outcome measure:

1. Measurable residual disease (MRD) status, collected on randomisation and then again immediately prior to transplant. A patient will be categorised as either MRD status reduction (MRD positive to negative), MRD remain negative, MRD remain positive or MRD progression (MRD negative to positive) – Randomisation 1 only

2. Disease-free survival defined as time from randomisation to the relevant question to the date of first relapse or death from any cause. Patients who are alive and disease free at the end of the trial will be censored at their date last known to be alive

3. Cumulative incidence of disease relapse defined as time from randomisation to the relevant question to the date of relapse. Patients who die prior to relapse will be treated as a competing risk and patients who are alive and relapse free at the end of the trial will be censored at their date last seen

4. Non-relapse mortality defined as the time from randomisation to date of non-relapse death. Patients who die post-relapse will be treated as a competing risk and patients who are alive at the end of the trial will be censored at their date last seen

5. Quality of life measured by EORTC-QLQ-C30 and EQ-5D questionnaires pre transplant, at day 28 and months 3, 6, 9, 12, 18 and 24 – Randomisations 2 and 3 only

6. Incidence of acute and chronic GVHD of any grade – Randomisations 2 and 3 only

7. Incidence of primary graft failure – Randomisations 2 and 3 only

8. Incidence of toxicities reported as per CTCAE V4.0 defined as the number of patients who report one or more AE of grade 3 or higher or an SAE of any grade

## **Completion date**

31/05/2026

## **Eligibility**

### **Key inclusion criteria**

Inclusion Criteria for Randomisation 1:

1. Patients ( $\geq 18$  years old) with a morphological documented diagnosis of AML or MDS who are deemed fit for allo-SCT with one of the following disease characteristics:

1.1. AML:

1.1.1. Patients in 1st complete remission (CR1) defined as  $< 5\%$  blasts

1.1.2. Patients in 2nd complete remission (CR2) defined as  $< 5\%$  blasts

1.1.3. Secondary AML (defined as previous history of MDS, antecedent haematological disease or

chemotherapy

exposure) in CR1 or 2 defined as < 5% blasts

1.2. MDS:

- 1.2.1 Patients with high risk MDS with an IPSS-R of  $\geq 3.5$  (intermediate 3.5 or higher) including intermediate or high risk CMML (e.g. CPSS int-2 or high risk)
2. Patients with an identified HLA identical sibling or suitable matched unrelated donor (suitable match defined as no greater than a single allele mismatch at HLA-A, -B, -C, DR $\beta$ 1 or DQB1 locus)
3. Patients must be considered suitable to undergo allo-SCT as clinically judged by the Local Investigator
4. Females of and male patients of reproductive potential (i.e., not post-menopausal or surgically sterilised) must use appropriate, highly effective, contraception from the point of commencing therapy until 6 months after treatment
5. Patients have given written informed consent
6. Patients willing and able to comply with scheduled study visits and laboratory tests

Inclusion Criteria for Randomisation 2:

1. Patients aged between 18 – 54 years with a morphological documented diagnosis of AML or MDS who are deemed fit for a MAC allo-SCT with one of the following disease characteristics:
  - 1.1. AML:
    - 1.1.1. Patients in 1st complete remission (CR1) defined as < 5% blasts
    - 1.1.2. Patients in 2nd complete remission (CR2) defined as < 5% blasts
    - 1.1.3. Secondary AML (defined as previous history of MDS, antecedent haematological disease or chemotherapy exposure) in CR1 or 2 defined as < 5% blasts
    - 1.1.4. Must have received at least two courses of prior intensive chemotherapy prior to transplant unless there are exceptional circumstances. Patients with AML who have achieved CR with Venetoclax based induction regimen treatment as only prior treatment, will also be eligible.
  - 1.2. MDS:
    - 1.2.1 Patients with advanced or high risk MDS (with an IPSS-R of  $\geq 3.5$  (intermediate 3.5 or higher) including intermediate or high risk CMML (e.g. CPSS int-2 or high risk) who have < 10% blasts at the time of randomisation following intensive chemotherapy (including R1 randomisation) or hypomethylating agents if necessary
    2. Patients with an identified HLA identical sibling or suitable matched unrelated donor (suitable match defined as no greater than a single allele mismatch at HLA-A, -B, -C DR $\beta$ 1, or DQB1 locus)
    3. Patients with an ECOG performance status of 0,1 or 2
    4. Patients considered suitable to undergo a MAC allo-SCT as clinically judged by the Local Investigator including:
      - 4.1. Adequate hepatic and renal function as determined by full blood count and biochemistry assessment
      - 4.2. Resolution of any toxic effects of prior therapy (including radiotherapy, chemotherapy or surgical procedures)
      - 4.3. Performance of cardiac or pulmonary function tests (where there is a previous history of cardiac or pulmonary impairment)
    5. Females of and male patients of reproductive potential (i.e., not post-menopausal or surgically sterilised) must use appropriate, highly effective, contraception from the point of commencing therapy until 12 months after treatment
    6. Patients have given written informed consent
    7. Patients willing and able to comply with scheduled study visits and laboratory tests

Inclusion Criteria for Randomisation 3:

1. Patients aged between 55 years or older with a morphological documented diagnosis of AML or MDS who are deemed fit for a RIC allo-SCT (or under the age of 55 with comorbidities which are deemed by the local investigator to preclude safe delivery of a MAC allo-SCT may be

considered per investigators discretion) with one of the following disease characteristics:

**1.1. AML**

1.1.1. Patients in 1st complete remission (CR1) defined as < 5% blasts

1.1.2. Patients in 2nd complete remission (CR2) defined as < 5% blasts

1.1.3. Secondary AML (defined as previous history of MDS, antecedent haematological disease or chemotherapy exposure) in CR1 or 2 defined as < 5% blasts

1.1.4. Must have received at least two courses of prior intensive chemotherapy prior to transplant unless there are exceptional circumstances. Patients with AML who have achieved CR with Venetoclax based induction regimen treatment, as only prior treatment, will also be eligible

**1.2. MDS**

1.2.1. Patients with high-risk MDS (with an IPSS-R of  $\geq 3.5$  (intermediate 3.5 or higher) including intermediate or high risk CMML (e.g. CPSS int-2 or high risk) who have < 10% blasts at the time of randomisation following intensive chemotherapy (including R1 randomisation) or hypomethylating agents if necessary

2. Patients with an identified HLA identical sibling or suitable matched unrelated donor (suitable match defined as no greater than a single allele mismatch at HLA-A, -B, -C, DR $\beta$ 1 or DQB1 locus)

3. Patients with an ECOG performance status of 0,1 or 2

4. Patients considered suitable to undergo a RIC allo-SCT as clinically judged by the Local Investigator including:

a. Adequate hepatic and renal function as determined by full blood count and biochemistry assessment

b. Resolution of any toxic effects of prior therapy (including radiotherapy, chemotherapy or surgical procedures)

c. Performance of cardiac or pulmonary function tests (where there is a previous history of cardiac or pulmonary impairment)

5. Females of and male patients of reproductive potential (i.e., not post-menopausal or surgically sterilised) must use appropriate, highly effective, contraception from the point of commencing therapy until 12 months after treatment

6. Patients have given written informed consent

7. Patients willing and able to comply with scheduled study visits and laboratory tests

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Total final enrolment**

333

**Key exclusion criteria**

Exclusion criteria for Randomisation 1 (R1):

1. Patients with contraindications to receiving allo-SCT
2. Female patients who are pregnant or breastfeeding. All women of childbearing potential must have a negative pregnancy test before commencing treatment
3. Adults of reproductive potential not willing to use appropriate, highly effective, contraception during the specified period
4. Patients with renal or hepatic impairment as clinically judged by the Local Investigator
5. Patients with active infection, HIV-positive or chronic active HBV or HCV.
6. Patients with a prior malignancy, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin or treated cervical carcinoma in situ, incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node, metastasis (TNM) clinical staging system), previous MDS, CMML, MPN resulting in secondary AML. Cancer treated with curative intent  $\geq 5$  years previously will be allowed. Cancer treated with curative intent  $< 5$  years previously will not be allowed.
7. History of serious hypersensitivity reaction to cytarabine, daunorubicin, or any component of the Vyxeos formulation.
8. Known history of Wilson's disease or other copper-related metabolic disorder since copper gluconate is a component of the Vyxeos formulation

Exclusion criteria for Randomisation 2 (R2):

1. Patients with contraindications to receiving a MAC allo-SCT
2. Female patients who are pregnant or breastfeeding. All women of childbearing potential must have a negative pregnancy test before commencing treatment
3. Adults of reproductive potential not willing to use appropriate, effective, contraception during the specified period
4. Patients with renal or hepatic impairment as clinically judged by the Local Investigator
5. Patients with active infection, HIV-positive or chronic active HBV or HCV
6. Patients with a prior malignancy, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin or treated cervical carcinoma in situ, incidental histologic finding of prostate cancer (T1a or T1b using the tumour, node, metastasis (TNM) clinical staging system), previous MDS, CMML, MPN resulting in secondary AML. Cancer treated with curative intent  $\geq 5$  years previously will be allowed. Cancer treated with curative intent  $< 5$  years previously will not be allowed.

Exclusion criteria for Randomisation 3 (R3):

1. Patients with contraindications to receiving a RIC allo-SCT
2. Female patients who are pregnant or breastfeeding. All women of childbearing potential must have a negative pregnancy test before commencing treatment
3. Adults of reproductive potential not willing to use appropriate, effective, contraception during the specified period
4. Patients with renal or hepatic impairment as clinically judged by the Local Investigator
5. Patients with active infection, HIV-positive or chronic active HBV or HCV
6. Patients with a prior malignancy, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin or treated cervical carcinoma in situ, incidental histologic finding of prostate cancer (T1a or T1b using the tumour, node, metastasis (TNM) clinical staging system), previous MDS, CMML, MPN resulting in secondary AML. Cancer treated with curative intent  $\geq 5$  years previously will be allowed. Cancer treated with curative intent  $< 5$  years previously will not be allowed.

**Date of first enrolment**

27/01/2020

**Date of final enrolment**

03/03/2023

**Locations****Countries of recruitment**

United Kingdom

England

Scotland

Wales

**Study participating centre****King's College Hospital**

London

United Kingdom

SE5 9RS

**Study participating centre****St James's University Hospital**

Leeds

United Kingdom

LS9 7TF

**Study participating centre****Manchester Royal Infirmary**

Manchester

United Kingdom

M13 9WL

**Study participating centre****Freeman Hospital**

Newcastle-Upon-Tyne

United Kingdom

NE7 7DN

**Study participating centre****Churchill Hospital**

Oxford

United Kingdom  
OX3 7LE

**Study participating centre**  
**Queen Elizabeth Hospital**  
Birmingham  
United Kingdom  
B15 2GW

**Study participating centre**  
**Bristol Haematology and Oncology Centre**  
Bristol  
United Kingdom  
BS2 8ED

**Study participating centre**  
**Addenbrookes Hospital**  
Cambridge  
United Kingdom  
CB2 0QQ

**Study participating centre**  
**University Hospital of Wales**  
Cardiff  
United Kingdom  
CF14 4XW

**Study participating centre**  
**Hammersmith Hospital**  
London  
United Kingdom  
W12 0HS

**Study participating centre**  
**Leicester Royal Infirmary**  
Leicester  
United Kingdom  
LE1 5WW

**Study participating centre**  
**Nottingham City Hospital**  
Nottingham  
United Kingdom  
NG5 1PB

**Study participating centre**  
**Derriford Hospital**  
Plymouth  
United Kingdom  
PL6 8DH

**Study participating centre**  
**Royal Hallamshire Hospital**  
Sheffield  
United Kingdom  
S5 7AU

**Study participating centre**  
**Southampton General Hospital**  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre**  
**Royal Stoke University Hospital**  
Stoke-on-Trent  
United Kingdom  
ST4 6QG

**Study participating centre**  
**ASST Papa Giovanni XXIII**  
BERGAMO  
Italy  
24127

**Sponsor information**

**Organisation**

University of Birmingham

**ROR**

<https://ror.org/03angcq70>

**Funder(s)****Funder type**

Charity

**Funder Name**

IMPACT (funded by NHS Blood & Transplant, Anthony Nolan and Leukaemia UK)

**Funder Name**

Jazz Pharmaceuticals

**Alternative Name(s)**

Jazz Pharmaceuticals plc, Greenwich Biosciences, Jazz Pharmaceuticals, Inc.

**Funding Body Type**

Government organisation

**Funding Body Subtype**

For-profit companies (industry)

**Location**

Ireland

**Funder Name**

ADIENNE SA

**Results and Publications****Individual participant data (IPD) sharing plan**

The data sharing plans for the current study are unknown and will be made available at a later date.

**IPD sharing plan summary**

Data sharing statement to be made available at a later date

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No