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Managing the use of antifungal drugs for blood cancer patients by using blood tests to identify fungal infection

Submission date
08/06/2022

Recruitment status
No longer recruiting

Registration date
24/06/2022

Overall study status
Ongoing

Last Edited
26/05/2026

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Acute myeloid leukaemia (AML), high risk myelodysplasia (HRMDS), and acute lymphoblastic leukaemia (ALL) are blood cancers treated by chemotherapy. Prolonged fever is common during chemotherapy and can be due to a fungal infection. This may be life-threatening and is difficult to diagnose. Antifungal drugs are often given as a preventive. Antifungals have side effects and overuse may lead to infections that are resistant to them. Alternatively, blood tests can be used to detect fungal infections before symptoms start.
The aim of this study is to determine if fewer antifungals are used in patients having regular blood tests compared to preventative antifungal drugs, without decreasing quality of life.

Who can participate?
Adult patients with a new diagnosis of, or relapsed, acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), or high-risk myelodysplasic syndrome (HRMDS) who need chemotherapy and have not had a previous proven or probable invasive fungal infection. Sites can volunteer to participate by completing an Expression of Interest form and then discussing if it is an appropriate site to run the study. Participating sites will invite patients who are eligible to participate.

What does the study involve?
Patients will be recruited from 21 hospitals and they will be allocated to one of these antifungal management groups by chance:
1. Blood tests for fungal infection twice a week. If these are positive or if the patient becomes ill in a way suggesting fungal infection, further tests will be recommended. Antifungals will be recommended if tests suggest a fungal infection is likely.
2. Preventive antifungal drugs. If the patient becomes ill, tests and therapeutic antifungal drugs will be given based on the opinion of the doctor in charge.
Antifungal management will continue for the duration of the patient's chemotherapy. Patients will be followed up with questionnaires at 3, 6 and 12 months after starting the study. The side effects, the number of fungal infections and deaths, and value for money for the NHS will be monitored. A process evaluation will be undertaken to evaluate how the intervention is

delivered and the experience of healthcare staff and patients.
Based on the results of this study, we will encourage hospitals to review their antifungal use.

What are the possible benefits and risks of participating?
There may be no benefit of taking part in the study to participants personally, but they will be helping to improve care for future patients with blood cancers.
Both approaches being compared in this study (i.e. preventative antifungal drugs or regular monitoring using blood tests) are used in the NHS already. Therefore, taking part in this study does not involve a higher risk than receiving antifungal treatments or blood monitoring as part of the participant's standard NHS care.

Where is the study run from?
Hull University Teaching Hospitals NHS Trust (UK)

When is the study starting and how long is it expected to run for?
From May 2022 to May 2027

Who is funding the study?
National Institute for Health and Care Research (UK)

Who is the main contact?
Dr Samantha Brady, biodrive-group@york.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-blood-test-to-reduce-the-use-of-fungal-medication-for-certain-blood-cancers

Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
306996

Central Portfolio Management System (CPMS)
52545

National Institute for Health and Care Research (NIHR)
132674

Protocol serial number
Grant Codes:

Study information

Scientific Title
Biomarker Driven Antifungal Stewardship (BioDriveAFS) in acute leukaemia – a multi-centre randomised controlled trial to assess clinical and cost effectiveness

Acronym
BioDriveAFS

Study objectives
Current study hypothesis as of 26/02/2025:

The intervention (a biomarker-based antifungal stewardship strategy) is not inferior to control (a prophylactic antifungal strategy, including existing standard of care), in reducing AF therapy use in patients with acute leukaemia (AML/ALL/HRMDS) undergoing chemotherapy, without adverse impact on health-related quality of life in the 12 months from trial enrolment.

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Previous study hypothesis:

The intervention (a biomarker-based antifungal stewardship strategy) is not inferior to control (a prophylactic antifungal strategy, including existing standard of care), in reducing AF therapy use in patients with acute leukaemia (AML/ALL/HRMDS) undergoing intensive chemotherapy, without adverse impact on health-related quality of life in the 12 months from trial enrolment

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/05/2022, South West - Frenchay Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, BS1 6PN; +44 (0)207 104 8379 ; frenchay.rec@hra.nhs.uk), ref: 22/SW/0053

Primary study design
Interventional

Study design
Multi-centre randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Fungal infection following treatment for acute myeloid leukaemia (AML), high risk myelodysplasia (HRMDS), and acute lymphoblastic leukaemia (ALL)

Interventions
Current interventions as of 26/02/2025:

Trial design:
The trial is designed as a multicentre, 404-patient, randomised controlled trial with parallel groups, of a biomarker-based antifungal stewardship (AFS) strategy versus a prophylactic antifungal (AF) strategy, including existing standard of care (SoC), in reducing AF therapy use in patients with acute leukaemia undergoing chemotherapy. The cost-effectiveness of these two strategies will also be compared. Blinding is not possible given the nature of the intervention.

Randomisation:
Randomisation will be implemented using the secure web-based data collection/management interface 'REDCap'. This system will be accessed by clinical research staff involved in patient recruitment at recruiting sites (as detailed in the site delegation log) and will be accessible 24 hours a day and 7 days a week. The allocation sequences (using block randomisation stratified by site, with randomly permuted block sizes) will be designed by the trial statistician. The actual sequences embedded in the randomisation system will be generated by a separate YTU statistician independent of the Trial Management Group, using a random number seed that will be concealed from all members of the trial team for the duration of the trial.

Intervention arm:
Participants allocated to the biomarker-based AFS strategy will be monitored for invasive fungal

infections (IFIs) with regular blood biomarker tests, combined with, when necessary (e.g. prolonged Neutropenic Fever (NF) and/or symptoms or signs), further responsive tests to identify patients likely to have IFI prior to directed AF therapy.

Control (SoC) arm:
Participants in the control arm must receive prophylactic AF therapy with a recognised anti-Aspergillus agent (posaconazole, itraconazole [only when one of the other azoles cannot be used], isavuconazole, voriconazole, liposomal amphotericin, or [when azoles cannot be used] anidulafungin, micafungin or caspofungin) can be used within the trial, fluconazole cannot be used. This is the current most common SoC approach to the prevention of IFI in neutropenic patients within the NHS, within the context of existing local SoC. No regular (surveillance) biomarkers will be allowed in this arm, although 'reactive' biomarker tests (i.e. when a patient is ill and IFI is a potential concern), of the clinical team's choice, can be performed according to usual local clinical practice. The exact dosing regimen used is at the discretion of the clinical team caring for the patient but should be in keeping with existing local, national or international guidance.

Following baseline assessments, and randomisation, participants will be monitored and treated for IFI via one of the two intervention strategies described, and will complete follow-up assessments at 3 months, 6 months, and 12 months post randomisation.

Internal Pilot and recruitment rate:
An internal pilot phase in a small number of centres will run during the first 9 months of the main trial, which will assess the assumptions about recruitment and provide guidance on optimising the trial processes. The proposed recruitment rate is based on a recruitment period of 30 months with 21 sites in total, to recruit 404 participants.

Sampling and sample sizes:
Patients will be screened for the study who are aged 16 or over who have a diagnosis or relapse of acute myeloid leukaemia (AML), high-risk myelodysplasic syndrome (HRMDS) or acute lymphoblastic leukaemia (ALL), who need chemotherapy. Patients will be identified at the point of diagnosis in participating NHS hospitals prior to beginning chemotherapy and approached about the trial by their treating clinical team. Only patients who are willing and able to give informed consent for participation in the study will be enrolled and they may request to leave the study at any time and without needing to provide the research team with a reason.
The sample size of 404 has been calculated based on the co-primary outcomes (antifungal therapy use and health-related quality of life) and the sufficiently powered secondary outcome (proven/ probable fungal infection).

Pragmatic design:
The trial is designed to be pragmatic and not to be a burden to patients, we intend to align interventions (i.e. blood tests) with inpatient care and regular hospital visits, which are common in AML/HRMDS/ALL patients having chemotherapy. Patients usually attend hospital at least once or twice weekly through the chemotherapy phase so travel to hospital for the purposes of the trial is not anticipated. Antifungal management will continue for the duration of the patients' chemotherapy treatment, whilst they are considered vulnerable to infections.
Both methods of antifungal management are currently used within the NHS, however most hospitals use preventative antifungals. There is a growing risk of antifungal resistance developing if antifungals are overused. It is not currently known if blood tests for fungal infection are as good as preventative antifungals for managing fungal infections in patients with AML/HRMDS/ALL. This study will directly compare the 2 management options to find out if blood tests are a better option than preventative antifungals. Blood tests will be considered a

better way of managing fungal infections if they reduce the use of therapeutic antifungals used without impacting on the patient's quality of life.

Process Evaluation:
The BioDriveAFS trial will integrate a mixed methods process evaluation in parallel to the internal pilot and full trial. This will focus on fidelity to the clinical pathway and barriers and facilitators to implementation. The quantitative assessment of fidelity to the clinical pathway will be based on data collected by research nurses on every patient, the majority of this information should be available in the patient's medical notes.
The qualitative assessment will aim to understand the context and explore implementation. Both healthcare staff and patients will take part in qualitative research during the internal pilot study and later in the main trial. Participation will be optional for patients and healthcare staff and consent will be sought separately to the main study. Interviews are likely to be a mixture of face to face, video or phone.
Healthcare staff:
A mixture of interviews and focus groups dependent on participant preference. The interview or focus group is likely to last around 30 to 40 minutes.
Patients:
The purpose is to understand patients' perceptions of the intervention and questioning will be participant led. The interview is likely to last between 40 – 60 minutes.
Lead clinician per site:
This will take the form of a brief, structured telephone interview lasting around 20 minutes.
After the pilot phase, mixed methods analyses will be used to make refinements to the treatment pathway/clinician
training to improve adherence moving forward into the main trial.

PPI perspective:
This is a complex topic and we have engaged a range of patients, carers, and advocates from different groups, including Leukaemia Care and Involvement@York, as well as patients from Hull University Teaching Hospitals (HUTH). To understand if the trial would answer the 'right' questions from a patient perspective and to understand how the trial would impact the lives of AML/ALL/HRMDS patients and their families, we hosted four PPI sessions to hear about their lived experiences from diagnosis to remission. Participants had personal experience of chemotherapy, the rigors of a cancer diagnosis and therapy for invasive fungal infection.
A high value was placed on leukaemia research and associated supportive care. Participants had a range of views on the merits of preventative antifungals with some stating that additional medications were a burden, but there was also appreciation of the risks of invasive fungal infection. With respect to our proposed intervention of blood tests for biomarker-based monitoring there was a high degree of acceptance for this approach as patients already endure frequent blood tests; having more blood taken was not considered excessive, especially if taken at the same time as other clinical blood tests.
With respect to our proposed endpoints of antifungal use, health-related quality of life (HRQoL) and invasive fungal infection, a high value was placed on HRQoL in relation to excessive oral medication. PPI events refined our approach in respect to the acceptability of our proposed intervention of a biomarker-based strategy and the relevance of the research topic to AML /HRMDS patients. Our proposed tool for assessing HRQoL (EQ-5D-5L) was felt to be acceptable and the visual analogue scale within the EQ-5D-5L was felt to be informative with regards to overall level of function.
Our coprimary outcomes, and the adequately powered secondary outcome of proven/probable invasive fungal infection, encompass the key priorities identified by engagement with both our PPI group and clinical stakeholders.

Parallel studies to BioDriveAFS:
Some sites will be invited to take part in the collection of additional blood samples from patients, this will be optional for patients at participating sites and will not affect their participation in the main study. Extra blood samples will be collected at the same time as other study blood samples.
In addition, some sites will be invited to collect other additional samples. This will be optional for patients and patient's participation in giving other additional samples does not affect their involvement in the main trial or to give additional blood samples. The other additional samples will include; faecal samples, skin/oral (swabs or wash) and breath samples, serial collections will be made no more than twice monthly.

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Intervention Type
Other

Primary outcome(s)

1. Antifungal (AF) exposure in the 12 months from recruitment, defined as receipt of ≥72 hours of therapeutic systemic AF, measured as a dichotomous variable (Yes/No) at 12 months
2. Health-related quality of life at 12 months post-randomisation measured using EuroQol 5 Dimensions (5L) Score (EQ-5D-5L) collected at 12 months

Key secondary outcome(s)

Current secondary outcome measures as of 24/04/2024:

1. Total antifungal (AF) exposure in the 12 months from recruitment measured using the total Defined Daily Doses (DDD) and whole days of therapy of prophylactic and therapeutic AF use at 12 months
2. Probable/proven invasive fungal infection (IFI) measured using clinical assessment of probable and proven IFIs as per the consensus definitions of the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group at 12 months
3. All-cause mortality, and invasive fungal infection (IFI) mortality measured using patient status data collected at 12 months
4. Invasive fungal infection (IFI) treatment outcomes measured using data on the outcome of IFI treatment (treatment given and completed with no relapse; treatment given and completed, but with relapse; ongoing treatment; and IFI-related mortality) collected at 12 months
5. Antifungal-associated adverse effects/events/complications, measured using the adverse event reporting procedure records, and/or from relevant follow-up case report forms as appropriate, between baseline and 12 months
6. Resource use measured using hospital care health service use (e.g. length of hospital inpatient stay, readmissions, and outpatient visits) and product cost data collected from hospital records on a monthly basis.
7. Episodes of neutropenic fever requiring hospital admission or outpatient management, measured using the standard ESMO Clinical Practice Guidelines definition at 12 months
8. Antifungal resistance in fungi (non-invasive and invasive) measured using fungi isolated from clinical specimens taken as part of routine care (additional samples will not be taken unless the patient has consented and the site is participating in additional sampling for storage/research) between baseline and 12 months. This will be reported to YTU for the 12 months from study recruitment.
9. Desirability of Outcome Ranking (DOOR) measured using data that will be collected throughout the 12-month follow-up period and ranked based on defined hierarchical levels that will be developed and confirmed following discussion with stakeholders, using Delphi methodology, and the Patient Advisory Group. It is anticipated that the hierarchical levels will take into account elements such as survival, presence of proven/probable IFI, and antifungals adverse effects/events.

Previous secondary outcome measures:

1. Total antifungal (AF) exposure in the 12 months from recruitment measured using the total Defined Daily Doses (DDD) and whole days of therapy of prophylactic and therapeutic AF use at 12 months
2. Probable/proven invasive fungal infection (IFI) measured using clinical assessment of probable and proven IFIs as per the consensus definitions of the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group at 12 months
3. Survival, all-cause mortality, and invasive fungal infection (IFI) mortality measured using

patient status data collected at 12 months
4. Invasive fungal infection (IFI) treatment outcomes measured using data on the outcome of IFI treatment (treatment given and completed with no relapse; treatment given and completed, but with relapse; ongoing treatment; and IFI related mortality) collected at 12 months
5. Antifungal associated adverse effects/events/complications, measured using the adverse event reporting procedure records, and/or from relevant follow-up case report forms as appropriate, between baseline and 12 months
6. Resource use measured using hospital care health service use (e.g. length of hospital inpatient stay, readmissions, and outpatient visits) and product cost data collected from hospital records and through patient questionnaires at 3, 6, and 12 months
7. Episodes of neutropenic fever requiring hospital admission or outpatient management, measured using the standard ESMO Clinical Practice Guidelines definition at 12 months
8. Antifungal resistance in fungi (non-invasive and invasive) measured using fungi isolated from clinical specimens taken as part of routine care (additional samples will not be taken unless the patient has consented and the site is participating in additional sampling for storage/research) between baseline and 12 months. This will be reported to YTU for the 12 months from study recruitment.
9. Desirability of Outcome Ranking (DOOR) measured using data that will be collected throughout the 12-month follow-up period and ranked based on defined hierarchical levels that will be developed and confirmed following discussion with stakeholders, using Delphi methodology, and the Patient Advisory Group. It is anticipated that the hierarchical levels will take into account elements such as survival, presence of proven/probable IFI, and antifungals adverse effects/events.

Completion date
31/05/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 26/02/2025:

1. Aged ≥16 years
2. Diagnosis of new, or relapsed, acute leukaemia or haematological disorder judged to need chemotherapy by the patient's clinical care team. Eligible conditions include acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), high-risk myelodysplastic syndrome (HRMDS), or AML transformation of a myeloproliferative neoplasm (tMPN).
3. The patient is expected to have prolonged neutropenia related to chemotherapy which would mandate either antifungal prophylaxis and/or systematic invasive fungal infection biomarker monitoring (at least weekly).
4. Patient is willing and able to give informed consent for participation in the study

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1. Aged ≥16 years
2. Diagnosis of new, or relapsed, acute leukaemia or haematological disorder judged to need intensive chemotherapy by the patient's clinical care team. Eligible conditions include acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), high-risk myelodysplastic syndrome (HRMDS), or AML transformation of a myeloproliferative neoplasm (tMPN).

3. The patient is expected to have prolonged neutropenia related to intensive chemotherapy which would mandate either antifungal prophylaxis and/or systematic invasive fungal infection biomarker monitoring (at least weekly).
4. Patient is willing and able to give informed consent for participation in the study

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Previous inclusion criteria:

1. Aged ≥16 years
2. New diagnosis of, or relapsed, acute myeloid leukaemia (AML; according to WHO classification), acute lymphoblastic leukaemia (ALL), or high-risk myelodysplasic syndrome (HRMDS) judged to need intensive chemotherapy by the patient's clinical care team
3. The patient is expected to have prolonged neutropenia (≥10 days) because of their intensive chemotherapy
4. Patient is willing and able to give informed consent for participation in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 26/02/2025:

1. Previous proven or probable invasive fungal infection (IFI) (according to the EORTC/MSG criteria). (I.e. this would not include previously treated cutaneous or other non-invasive infection, etc. If there is doubt about eligibility, please discuss with the local PI / research team and, if required, the central trial team / Chief Investigators).
2. Contraindication to all potential prophylactic antifungal agents (i.e. cannot be prescribed any recognised anti-Aspergillus agent as prophylaxis)
3. Planned chemotherapy using any regimen that mandates the use of systemic antifungal medication
4. Received > 72 hours of systemic mould-acting antifungal prophylaxis or therapy, or biomarker monitoring for IFI, prior to trial enrolment

5. Commenced the first cycle of chemotherapy > 72 hours prior to trial enrolment
6. Current diagnosis of prolonged (> 72 hours) neutropenic fever
7. Pregnancy

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Previous exclusion criteria as of 24/04/2024:

1. Previous proven or probable invasive fungal infection (IFI) (according to the EORTC/MSG criteria). (I.e. this would not include previously treated cutaneous or other non-invasive infection, etc. If there is doubt about eligibility, please discuss with the local PI/research team and, if required, the central trial team / Chief Investigators).
2. Contraindication to all potential prophylactic antifungal agents (i.e. cannot be prescribed any recognised anti-Aspergillus agent as prophylaxis)
3. Planned chemotherapy using any regimen that mandates the use of systemic antifungal medication (i.e.Venetoclax-based regimens)
4. Received > 72 hours of systemic mould-acting antifungal prophylaxis or therapy, or biomarker monitoring for IFI, prior to trial enrolment
5. Commenced the first cycle of chemotherapy > 72 hours prior to trial enrolment
6. Current diagnosis of prolonged (> 72 hours) neutropenic fever
7. Pregnancy

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Previous exclusion criteria as of 26/05/2023:

1. Previous proven or probable invasive fungal infection (IFI)
2. Contraindication to all potential prophylactic antifungal agents (i.e. cannot be prescribed any recognised anti-Aspergillus agent as prophylaxis)
3. Planned chemotherapy using any regimen that mandates the use of systemic antifungal medication (i.e.Venetoclax-based regimens)
4. Commenced antifungal prophylaxis or biomarker monitoring for IFI
5. Commenced the first cycle of chemotherapy AND has entered the invasive fungal infection (IFI) at risk period according to the usual local standard of care (i.e. the period that normally mandates local IFIpreventi on measures such as antifungal prophylaxis and/or biomarker monitoring)
6. Current diagnosis of neutropenic fever
7. Pregnancy

Previous exclusion criteria:
1. Previous proven or probable invasive fungal infection (IFI)
2. Contraindication to all potential prophylactic antifungal agents (i.e. cannot be prescribed any recognised anti-Aspergillus agent)
3. Current diagnosis of chemotherapy-related neutropenic fever
4. Pregnancy
5. Planned chemotherapy using a Venetoclax based regimen mandating posaconazole as a concurrent medication

Date of first enrolment
25/07/2022

Date of final enrolment

31/05/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Hull University Teaching Hospitals NHS Trust
Hull Royal Infirmary
Anlaby Road
Hull
England
HU3 2JZ

Study participating centre
Mid Yorkshire Hospitals NHS Trust
Aberford Road
Wakefield
England
WF1 4DG

Study participating centre
Kings College Hospital
Denmark Hill
London
England
SE5 9RS

Study participating centre
Imperial College Healthcare NHS Trust
St Marys NHS Trust
Praed Street
London
England
W2 1NY

Study participating centre
Clatterbridge Cancer Centre
65 Pembroke PLACE
Liverpool
England
L7 8YA

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
England
NW1 2PG

Study participating centre
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Study participating centre
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Sponsor information

Organisation
Hull University Teaching Hospitals NHS Trust

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository and requests for access to data will be reviewed by the Chief Investigators, Study Sponsor, and York Trials Unit

IPD sharing plan summary

Available on request, Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		28/06/2024	01/07/2024	Yes	No
HRA research summary			26/07/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes