Full study title: **Biomarker Driven Antifungal Stewardship (BioDriveAFS) in Acute Leukaemia – a Multi-Centre Randomised Controlled Trial to Assess Clinical and Cost Effectiveness**

Short title**:** Biomarker Driven Antifungal Stewardship: The BioDriveAFS Trial

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# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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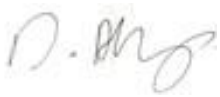
| Signature:  ..... | | Date: 20/01/2025 |

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# 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AF | Antifungal |
| AFS | Antifungal Stewardship |
| ALL | Acute Lymphoblastic Leukaemia |
| AML | Acute Myeloid Leukaemia |
| AML-SCS | AML Supportive Care Sub-Group of the National Cancer Research Institute |
| AMR | Antimicrobial resistance |
| AR | Adverse Reaction |
| BAL | Broncho-alveolar lavage |
| BG | Beta-D-glucan (biomarker) |
| BSAC | British Society for Antimicrobial Chemotherapy |
| CA | Competent Authority |
| CI | Chief Investigator |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| HRCT | High resolution computed tomography |
| CTA | Clinical Trial Authorisation |
| CTIMP | Clinical Trial of Investigational Medicinal Product |
| CTU | Clinical Trials Unit |
| DMEC | Data Monitoring and Ethics Committee |
| DSUR | Development Safety Update Report |
| EC | European Commission |
| EMEA | European Medicines Agency |
| EORTC/MSG | European Organization for Research and Treatment of Cancer and the Mycoses Study Group |
| EQ-5D-5L | EuroQol Quality of Life Measure |
| EU | European Union |
| EUCTD | European Clinical Trials Directive |
| EudraCT | European Clinical Trials Database |
| EudraVIGILANCE | European database for Pharmacovigilance |
| GCP | Good Clinical Practice |
| GM | Galactomannan (biomarker) |
| GMP | Good Manufacturing Practice |
| GP | General Practitioner |
| HRMDS | High Risk Myelodysplastic Syndromes |
| HRQoL | Health-Related Quality of Life |
| HYMS | Hull York Medical School |
| IA | Invasive Aspergillosis |
| IB | Investigator Brochure |
| IC | Intensive Chemotherapy |
| ICF | Informed Consent Form |

| | |
|---|---|
| ICH | International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use |
| IFI | Invasive Fungal Infection |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| ISF | Investigator Site File (This forms part of the trial master file) |
| ISRCTN | International Standard Randomised Controlled Trials Number |
| IV | Intravenous |
| MA | Marketing Authorisation |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MS | Member State |
| NF | Neutropenic Fever |
| NHS R&D | National Health Service Research & Development |
| NIMP | Non-Investigational Medicinal Product |
| PCR | Polymerase chain reaction |
| PI | Principal Investigator |
| PIC | Participant Identification Centre |
| PIS | Participant Information Sheet |
| QA | Quality Assurance |
| QC | Quality Control |
| QP | Qualified Person |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SDV | Source Data Verification |
| SoC | Standard of Care |
| SOP | Standard Operating Procedure |
| SmPC | Summary of Product Characteristics |
| SSI | Site Specific Information |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| tMPN | Acute myeloid leukaemia transformation of myelopreoliferative neoplasm (myeloproliferative neoplasms with disease progression to AML) |
| TSC | Trial Steering Committee |
| VAS | Visual Analogue Scale |
| YTU | York Trials Unit |

# 2 TRIAL SUMMARY

| | |
|---|---|
| Trial Title | Biomarker Driven Antifungal Stewardship (BioDriveAFS) in Acute Leukaemia – a Multi-Centre Randomised Controlled Trial to Assess Clinical and Cost Effectiveness |
| Short title | Biomarker Driven Antifungal Stewardship: The BioDriveAFS Trial |
| Clinical Phase | Phase III |
| Trial Design | Multi-centre open label randomised controlled trial |
| Objectives | 1) A multicentre two-arm open RCT to assess whether a biomarker antifungal stewardship (AFS) based strategy is superior to prophylactic antifungal (AF)/Standard of Care (SoC) with respect to therapeutic AF use, and non-inferior with respect to health-related quality of life (HRQoL) in adults (≥16 years) with AML, ALL or HRMDS undergoing chemotherapy<br>2) A 9-month internal pilot to assess capacity to recruit, randomise and retain participants; and optimise study processes prior to wider recruitment<br>3) Economic analyses to establish the costs of the two approaches and link these to primary outcomes<br>4) A mixed methods process evaluation to understand context and assess fidelity, and inform post-trial implementation strategy<br>5) Sustainable training and engagement to complement dissemination/ implementation |
| Trial Participants | Adults (≥16 years) with AML or ALL or HRMDS or tMPN undergoing chemotherapy |
| Intervention | Biomarker (twice weekly galactomannan and beta-D-glucan blood tests during periods of risk) and diagnostic based prevention and management of invasive fungal infections. During periods of lower risk (as deemed by the clinical care team), when a patient is being seem via outpatient clinics, testing can be reduced to a minimum of once weekly. |
| Control | Antifungal prophylaxis with an agent with recognised anti-Aspergillus species activity administered in the manner and dose consistent with usual clinical practice in the context of otherwise existing standard of care (but without regular biomarker testing; reactive diagnostic testing when a patient is unwell (e.g. neutropenic fever) according to usual local clinical practice is still allowed) |
| Planned Sample Size | 404 |
| Treatment duration | Period of risk for invasive fungal infection (IFI) |
| Follow up duration | 12 months from study entry |
| Planned Trial Period | 15th May 2022 to 31st May 2025 (end of recruitment) and 30th August 2025 (end of follow up) |

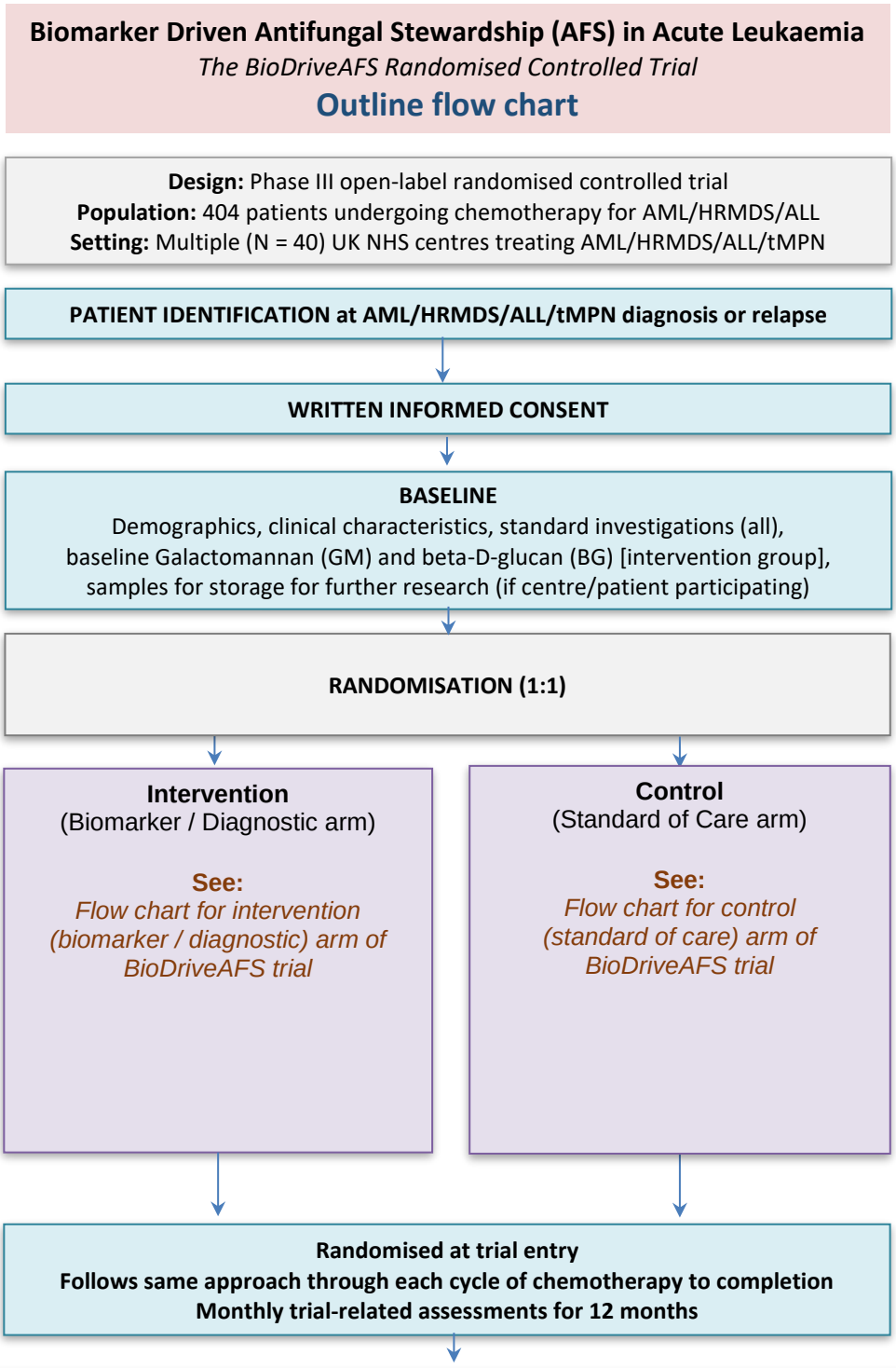
| Outcome Measures: | |
|---|---|
| Primary | *Co-primary endpoints:*<br>1) AF exposure defined as receipt of ≥72 hours or more of therapeutic systemic AF in the 12 months from trial entry<br>2) HRQoL as measured by the EQ-5D-5L at 12 months from trial entry |
| Secondary | *Adequately powered key secondary endpoint:*<br>3) Probable/proven IFI<br><br>*Other endpoints:*<br>4) Total AF exposure defined as: Total defined daily doses (WHO defined [1]) of prophylactic / therapeutic AF (separate therapeutic, prophylaxis and total AF analyses will be performed)<br>5) All cause and IFI related mortality<br>6) IFI treatment outcome by end of follow-up (treatment given and completed with no relapse; ongoing treatment; treatment given and completed, but with relapse; IFI related mortality)<br>7) AF associated adverse effects/events<br>8) Total length of hospital inpatient stay, readmissions and outpatient visits<br>9) Episodes of neutropenic fever* requiring admission to hospital (*standard definition [2])<br>10) Antifungal resistance in fungi (non-invasive and invasive) isolated from clinical specimens taken as part of routine care (i.e. additional samples will not be taken other than for patients consented for parallel studies – see below)<br><br>*Exploratory secondary endpoint:*<br>11) Desirability of Outcome Ranking (DOOR) [3] by proposed hierarchical levels to be developed following discussion with stakeholders, using Delphi methodology [4], and our patient advisory group (PAG) |
| Investigational Medicinal Product(s) | This trial is not investigating an investigational medicinal product. This has been confirmed with the MHRA. |



| KEY WORDS: | Acute leukaemia; Galactomannan; Beta-D-Glucan; Antifungal stewardship; Invasive fungal infection; Aspergillosis |
|---|---|

# 3 TRIAL FLOW CHARTS

## 3.1 Trial outline flow chart




**Primary endpoints:**

Exposure to therapeutic systemic AF therapy in the 12 months from trial entry (at least =>3 full days)

Patient quality of life (EQ-5D-5L) at 12 months versus baseline (also measured at 3 & 6 months)

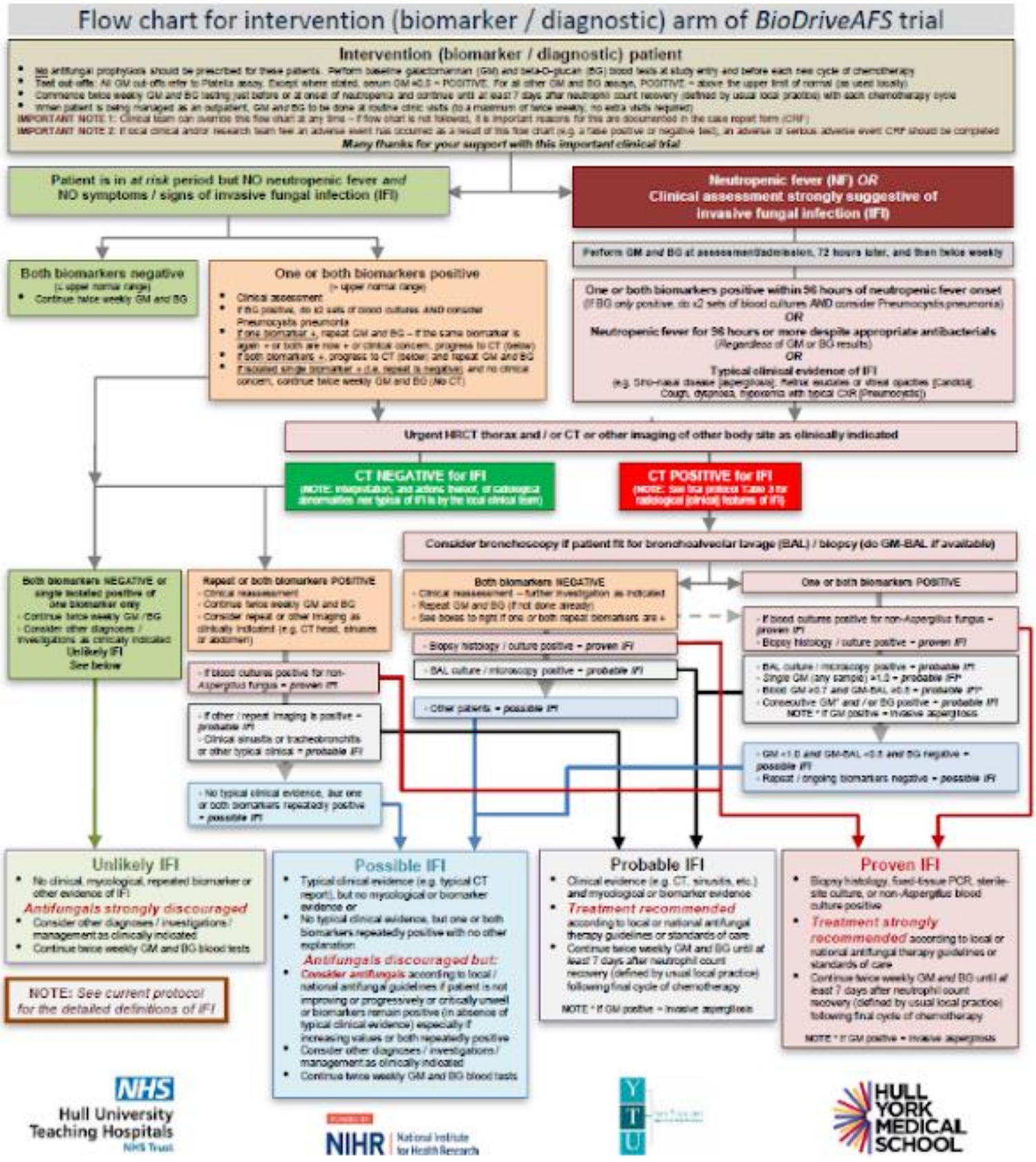
**Secondary endpoints:**

Survival at 12 months, all-cause mortality, diagnosis of probable/proven IFI, IFI associated mortality, adverse events and effects, total length of hospital stay, total prophylactic/systemic antifungal use

Cost-effectiveness: of biomarker driven AFS strategy compared to prophylactic AF

### 3.2 Flow Chart For Intervention (Biomarker / Diagnostic) Arm

A high-resolution version of the latest flowchart will be provided to recruiting sites separately.



### 3.3 Flow Chart for Control (Standard of Care) Arm

**Flow chart for control (standard of care) arm of *BioDriveAFS* trial**

**Control (standard of care) patient**

- Prophylactic antifungal prescribed according to local *usual* clinical practice or national or international guidance commenced at start of chemotherapy and subsequently discontinued when neutrophils >0.5 x $10^9$/L (>500 cells/$mm^3$) or as per *usual* local clinical practice
- The prophylactic agent *must* be a recognised anti-Aspergillus agent such as posaconazole, isavuconazole, voriconazole or itraconazole (the latter only when one of the other azoles cannot be used); or liposomal amphotericin; or (when azoles cannot be used) anidulafungin, caspofungin or micafungin **NOTE:** Fluconazole *cannot* be used as the prophylactic agent
- Exact dosing of the chosen agent is at the discretion of the clinical team caring for the patient, but should be in keeping with *usual* local clinical practice or national or international guidance. Therapeutic drug monitoring should reflect usual local practice for the antifungal being used.
- Use of biomarkers is allowed ***only*** if patient is unwell and invasive fungal infection suspected according to ***usual*** local clinical practice (i.e. serial weekly or twice biomarker testing is ***not*** allowed, but 'reactive' testing using biomarkers according to ***usual*** local clinical practice during illness when invasive fungal infection is suspected is allowed)
- **If fever >96 hours** despite antibacterials, investigate according to *usual* local standard of care clinical practice / guidelines / clinical team discretion
- Empiric antifungal therapy at the local clinical team's discretion
- Otherwise, management according to *usual* local clinical practice

**NOTE:** In the context of this trial, the term "standard of care" reflects the most common UK standard of care, which is use of antifungal prophylaxis without systematic biomarker testing during periods of risk. Some centres use both strategies together. To participate, such centres must be willing to adhere to the assigned intervention or control (standard of care) as outlined in this protocol (i.e. not to use systematic biomarker testing if a patient is assigned to the control [standard of care] arm of the trial).

# 4 BACKGROUND AND RATIONALE

## 4.1 About acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), high-risk myelodysplastic syndromes (HRMDS), and AML transformation of myeloproliferative neoplasms (tMPN).

Acute myeloid leukaemia (AML) is a blood cancer, potentially curable with chemotherapy [5], with approximately 3200 new cases diagnosed in the UK each year, 60% of which are in adults <75 years old [2]. The incidence of AML is increasing in the UK and is higher in males from deprived areas [6]. Myelodysplastic syndromes (MDS) are a group of diverse haematological disorders characterised by bone marrow dysfunction and with an estimated overall incidence of 4 per 100,000 citizens in the UK but increasing notably with age [7]. A proportion of patients with MDS are categorised as being high risk (HRMDS) for progression to AML and are therefore often treated similarly to AML with chemotherapy [8]. Acute lymphoblastic leukaemia (ALL) is a less common haematological cancer, which is relatively rare with an incidence of approximately 133 cases per year in adults in the UK [9], more commonly in males [10]. Patients with myeloproliferative neoplasms such as essential thrombocythaemia, polycythaemia rubra vera or chronic myelomonocytic leukaemia who experience disease progression to AML (tMPN) are also sometimes treated with chemotherapy in line with the approach for *de-novo* AML[11].

## 4.2 Invasive fungal infection in AML, ALL and HRMDS patients

Treatment of AML with intensive chemotherapy (IC) results in 60% survival at two years, but 30-day treatment mortality is 4-6% [5]. IC causes profound bone marrow suppression and as a result prolonged pancytopenia – a decrease in all three peripheral blood cell lines (erythrocytes, platelets and leukocytes), leading to an increased risk of neutropenic fever (NF) [5]. NF is often due to bacterial infection, but when NF is prolonged (=>96 hours), and not responsive to standard antibacterial regimens, the risk of invasive fungal infection (IFI) as the cause increases. The incidence of IFI in patients with AML/HMRDS/ALL/tMPN undergoing chemotherapy depends on various condition, patient and treatment factors, but is in the range of 4 to 11% [12], which is mostly due to invasive aspergillosis (IA) of the lungs and is associated with high mortality [13]. Invasive candidiasis also occurs in this group of patients, but is less common when AF prophylaxis is used [14].
The treatment of AML has changed over the past five years with the use of targeted agents for a subset of patients. Such agents include venetoclax, ivosidenib, midostaurine, quizartinib and gilteritinib. These targeted agents are either given in combination with other agents or as monotherapy. These agents are associated with an increased risk of IFI but estimates of this risk vary considerably [15].

## 4.3 Current management strategies for invasive fungal infections in the UK

Pulmonary invasive aspergillosis (IA) is difficult to diagnose and requires high-quality lung tissue samples from a bronchoscopy and alveolar lavage (BAL) or biopsy for an accurate diagnosis [16]. This can sometimes be difficult in ill AML/HRMDS/ALL/tMPN patients due to the risk of respiratory deterioration during the procedure and bleeding. IA is usually suspected clinically based on host-factors such as neutropenia, fever unresponsive to broad-spectrum antibiotics and radiological tests, before a proven or probable diagnosis can be made based on mycological (fungal) and other tests.

AML/HRMDS/ALL/ tMPN patients with possible IFI, especially during periods of prolonged NF, are often treated with systemic intravenous (IV) antifungals (AF), but a much lower proportion of such patients actually have proven or probable IFI, according to commonly used definitions [17], suggesting many patients do not need AF therapy [18]. To reduce IA in AML/HRMDS/ALL/ tMPN, AF prophylaxis is often prescribed during treatment [19]. In a UK national survey of clinical stakeholders performed during trial design, with help from the British Society for Antimicrobial Chemotherapy (BSAC) and the AML Supportive Care Sub-Group of the National Cancer Research Institute (AML-SCS), 80% of respondents stated their organisation use AF prophylaxis for AML patients. Of those, two-thirds use posaconazole.

It was clear from the above survey that not all UK centres use AF prophylaxis, however, and that some centres use a diagnostics approach, in keeping with the published literature. A diagnostics-driven approach to the prevention and management of IFI in this group of patients is an alternative to AF prophylaxis and reactive tests when patients are ill with NF. This involves monitoring for IFI with blood tests (biomarkers) combined with, when necessary, further responsive tests to identify patients likely to have IFI prior to targeted AF therapy. The two most commonly used biomarkers in the UK, currently mainly used reactively when patients become unwell, are galactomannan (GM) and beta-D-glucan (BG) [20, 21]. Both have moderate performance characteristics for the diagnosis of IFI when used alone [20, 21]. GM is more specific for IA, but BG can also identify other IFIs [22], including invasive candidiasis. The latter characteristic of BG may be important if AF prophylaxis is not prescribed. This was raised as a concern in our survey, although most respondents (78%) were still willing to be contacted about contributing to this trial. The performance characteristics of GM/BG raise the possibility of a combined approach for the early identification of IFI, but there is limited high-quality evidence comparing such an approach to the existing SoC in most UK centres.

AF therapy without a clear diagnosis remains the predominant strategy to combat IFI in AML patients with prolonged NF in the UK, although a sizable minority (36%) in our survey also appear to be using a diagnostics-driven approach at this stage of the care pathway, indicative of the existing and unsatisfactory variation in clinical practice recognised in the UK [19, 22-24]. A UK study of a diagnostics-led antifungal stewardship (AFS) programme, with haematology-oncology as the highest prescribers, found 40% of AF use was empiric with 82% without evidence of IFI. This programme reduced AF associated use and costs compared to national prevailing trends without impacting on mortality [23]. An AFS programme in Spain also reduced AF use without impacting the incidence of IFI or mortality [25].

Posaconazole (an AF) was shown to be superior to fluconazole/itraconazole (other antifungals) in preventing IFI in those with neutropenia when used prophylactically [18]. Posaconazole was associated with serious adverse events in 6% of patients, however, versus 2% with fluconazole/itraconazole. This pivotal trial currently underpins posaconazole prophylaxis as the standard of care (SoC) in the prevention of IFI in neutropenic patients in most UK centres, although only 2% and 8% of patients in the posaconazole and fluconazole/itraconazole arms, respectively, were diagnosed with proven/probable IFI, while 27% and 38%, respectively, still received empiric AF therapy during periods of illness (i.e. 25-30% of patients received unnecessary empiric AF therapy). Mortality due to IFI in this study was 2% and 5%, respectively, in the two arms. It is important to highlight that while posaconazole prophylaxis is now considered a SoC in AML/HRMDS/tMPN patients receiving IC, this assumption is based on comparison to fluconazole/itraconazole rather than a large clinical trial comparing it with a biomarker/diagnostics approach. The proportion of patients diagnosed with proven/probable IFI in the above trial was similar to that in a large systematic review of the

burden of IA in patients with haematological malignancy [12]. In the context of prolonged NF in AML/HRMDS, in our survey, 58% stated they prescribed empiric AF therapy.

### 4.4 Antifungal resistance

There is growing concern about resistance to the limited number and classes of AF agents [26]. The latter is exemplified by *Candida auris* as an easily transmissible multi-drug resistant pathogen, but resistance is increasing in other fungi, including in Aspergillus species [27]. As all AF use is likely to contribute to resistance across a wide range of fungal pathogens, optimising use will minimise risk. Cost-savings associated with lower AF use could also be invested in other high NHS priority areas.

### 4.5 Cost implications

Patients with AML/ALL/HRMDS/tMPN receiving chemotherapy and prophylactic antifungal therapy for IFIs account for a large portion of patients within the NHS receiving systemic antifungals. A service evaluation was performed to inform this application in the Department of Haematology at Hull University Teaching Hospitals (HUTH), which serves a regional population of 950,000. It highlighted that AML/HRMDS patients are very likely to be the key patient group driving AF use and costs within haematology departments in most (non-transplant) NHS hospitals, as well as being a key patient group to target to optimise AF prescribing within hospitals.

We found that over 12 months, 45 patients received at least one dose of liposomal amphotericin or voriconazole, which are the first line treatments for IFI at HUTH. AML/HRMDS patients accounted for 80% of these prescriptions. Over 51 consecutive months, the mean monthly use of AF was 1051 defined daily doses (DDD) with 60% in haematology-oncology (88% of which was in haematology). In 2019, systemic AF therapy cost HUTH £281,158 of which 72% was in haematology-oncology with liposomal amphotericin and posaconazole commonly prescribed as empiric and prophylactic AF respectively, accounting for 41% and 25% of total trust AF costs. An AF Commissioning for Quality and Innovation scheme was introduced in England in 2019, but was abandoned due to COVID-19 [26].

Treatment of IFI is associated with high costs [28], but there is evidence of potential cost-savings with a test-driven approach [29-31]. There is little evidence on cost-effectiveness [32]. A recent economic analysis from Australia suggested a biomarker approach can be cost-effective if a survival benefit is maintained long-term [33]. Assessing cost-effectiveness is important to support clinical policy decisions in the NHS (Section 14.5).

### 4.6 Rationale for BioDriveAFS Trial

A biomarker-driven approach to IFI in immunocompromised patients has been shown to reduce empiric AF use from 35% to 8% and 32% to 15% [29, 30]. In the trial by Morrisey et al (N = 240), the incidence of proven IFI and all-cause and invasive aspergillosis associated mortality was equivalent in the biomarker and SoC arms, although the diagnosis of probable IFI was statistically significantly higher in the biomarker group [30]. These studies suggest diagnostic driven approaches to AF use and IFI in high-risk groups can be effective and safe, but a large, more definitive trial in the context of NHS practice and diagnostic and other resources is required to provide the clinical evidence-base for UK policy change.

The use of a second biomarker for IFI improves diagnostic performance and is feasible [19, 34, 35]. GM can also be used on BAL specimens with moderate performance and we have therefore included it in our suggested algorithm for patients undergoing BAL [36]. The availability of this at a centre, however, does not preclude participation providing GM and BG blood tests can be accessed for included patients.

Systematic reviews suggest non-culture-based tests (GM, BG and Aspergillus PCR) when used alone for the diagnosis of IA/IFI perform similarly. Zhang et al assessed the performance of GM plus BG (combined). Of 7 studies, 6 were of combined blood tests and 4 in neutropenic patients [35]. If 1 out of 2 tests was positive, the probability of IA was x3.6. When both were negative, the probability was only 2%. The studies by Pazos et al and Pini et al suggest BG becomes positive before GM in IA [37, 38]. Pazos et al showed BG and GM typically became positive 5 and 11 (BG) and 4 and 9 (GM) days prior to fever and other symptom onset, respectively [37]. This suggests that even with a prolonged turnaround time for these tests, they can still usefully contribute to a diagnostics (biomarker) surveillance approach to the prevention of IFI. A UK study also suggested that a twice weekly combined blood diagnostic approach to IFI is safe and results in low empiric AF prescribing in high-risk patients [19]. The evidence therefore suggests that a combined blood biomarker approach may reduce AF use while identifying most patients at risk of IFI thereby allowing early investigation and directed AF therapy.

Most NHS laboratories are able to provide GM and BG testing either in-house or by sending samples elsewhere (96% and 89%, respectively) [24]. A GM/BG approach also has the advantage that BG may identify non-IA IFI (e.g. invasive candidiasis), which, while less common, still occurs (1-2% when taking prophylaxis) [18, 19]. As sampling will be twice weekly for inpatients, we will be able to analyse whether once versus twice weekly and one versus two biomarkers add incremental value (GM versus BG).

Although there is an increasing evidence-base for the use of Aspergillus PCR [39], including when combined with GM [34], it is less available, standardised and used in the UK. It is also less familiar to UK healthcare professionals, as demonstrated by the published literature [24] and our survey, which suggested only 31% of respondents used Aspergillus PCR in the context of prolonged NF in AML/HRMDS patients versus 62.5% and 54.0% for GM and BG, respectively. Aspergillus PCR was available to 56% of respondents versus 78% and 75% for GM and BG. This suggests GM and BG are the priority IFI biomarkers for investigation for any trial that aims to assess biomarkers that are currently widely available to the NHS and could be implemented rapidly following positive trial results in a high proportion of UK haematology departments.

Given the above, and the current pace of change in diagnostics research, especially during the pandemic, and after discussion with the AML-SCS who highlighted the need for further collaborative research in this neglected field and the opportunity that this trial presents, we will also store additional blood samples and / or left-over blood from biomarker testing from recruited patients for future research (this component is optional for both centres and patients).

Demonstrating the effectiveness of a biomarker driven AFS intervention in AML/HRMDS patients is therefore likely to reduce overall AF use and costs for the NHS as well as being an exemplar for other cohorts of patients at risk of IFI. The BioDriveAFS trial is a pragmatic randomised controlled trial (RCT), in the context of existing NHS clinical practices and procedures and targeting the entire care pathway for AF use, comparing the existing SoC in most centres (as described) to a proposed

combination biomarker/diagnostics driven approach to the prevention and treatment of IFI in adult AML/ALL/HRMDS/tMPN patients. The trial will use the co-primary endpoints of systemic AF therapy exposure and health-related quality of life (HRQoL), plus an adequately powered key secondary endpoint of proven/probable IFI, which were identified as the endpoints of most importance to patients and clinical stakeholders.

# 5 OBJECTIVES

## 5.1 Primary objective

To conduct a multicentre RCT to investigate whether a biomarker-based antifungal stewardship (AFS) strategy is superior to a prophylactic antifungal (AF) strategy, including existing standard of care (SoC), in reducing AF therapy use in patients with acute leukaemia (AML/ALL/HRMDS/tMPN) undergoing chemotherapy, without adverse impact on health-related quality of life (HRQoL) in the 12 months from trial enrolment.

## 5.2 Secondary objectives

- To conduct a 9-month internal pilot to assess trial feasibility and to optimise processes for trial continuation

- To conduct a mixed methods process evaluation alongside the RCT, focusing on assessment of fidelity and implementation via qualitative methods and clinical data collection. Findings will inform ongoing feedback to local research teams and potential amendments to trial processes and training as appropriate; and will subsequently inform dissemination and implementation plans within the NHS as appropriate

- To investigate the cost-effectiveness of a biomarker driven AFS strategy compared to prophylactic AF within the existing local SoC

- To develop and strengthen a sustainable training, engagement and Patient and Public Involvement legacy along with a network of engaged stakeholders

# 6 TRIAL DESIGN

## 6.1 Summary of BioDrive AFS trial design

The BioDriveAFS trial is 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.

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. Further details are given in Sections 6.3 and 14.3.

The BioDriveAFS trial will integrate a mixed methods process evaluation in parallel to the internal pilot and full trial, which is detailed in Section 7. This will focus on fidelity to the clinical pathway and barriers and facilitators to site trial participation and implementation.

*Intervention arm:* Participants allocated to the biomarker based AFS strategy will be monitored for invasive fungal infections (IFIs) with regular blood biomarker tests (GM and BG), combined with, when necessary (e.g. prolonged NF and/or symptoms or signs), further responsive tests, according to the intervention flow chart, 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 and/or other 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, and the need for and response to therapeutic drug monitoring, is at the discretion of the clinical team caring for the patient but should be in keeping with existing local, national or international practice or 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. Flow diagrams demonstrating the patient pathway through the study are presented in Section 3.

The study will be managed by York Trials Unit (YTU).

## 6.2 Primary and secondary outcome measures/endpoints

A co-primary endpoint will be used. Core outcomes have not been published for IFI or AML/HRMDS/ALL/tMPN, although the HARMONY Alliance is currently developing core outcomes for AML [40]. Suggested metrics (including outcomes) for AFS have been published and as such it has been ensured that the approach (detailed below) is consistent with these [41]. We have also included

an exploratory desirability of outcome ranking (DOOR) endpoint to assess relevance and how it is associated with other outcomes in this trial [3].

### *6.2.1 Co-primary outcome measures/endpoint*

- Antifungal (AF) exposure in the 12 months post-randomisation: This is defined as receipt of ≥72 hours of *therapeutic* systemic AF. Data on AF exposure will be reported to the YTU monthly by research staff at recruiting sites, based on electronic or paper drug charts, throughout the study via the case report form (CRF).

- EQ-5D-5L at 12 months post-randomisation: The EQ-5D-5L measures health-related quality of life in terms of 5 dimensions: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. Each dimension has five possible responses (no problems, slight problems, moderate problems, severe problems and unable or extreme problems). The EQ-5D-5L will be scored according to the User Guide [42]. EQ-5D-5L data will be collected via patient questionnaires by site research staff at baseline and then at 3, 6 and 12 months post-randomisation.

### *6.2.2 Secondary outcome measure/endpoint*

- Total antifungal (AF) exposure: The total Defined Daily Doses (DDD [1]) and whole days of therapy of prophylactic and therapeutic AF use. Data on AF exposure will be reported to YTU monthly for the 12 months from study entry by research staff at recruiting sites, based on electronic or paper drug charts, via the case report form (CRF).

- Probable/proven invasive fungal infection (IFI): Assessment of probable and proven IFIs will be 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 [17] (see Section 11.5). The same definitions will be used to define IFI in both arms of the trial. This will be reported to YTU monthly for the 12 months from study entry by research staff at recruiting sites, based on electronic or paper case notes, via the CRF.

- Survival: all-cause mortality and IFI mortality: This will be reported to YTU monthly for the 12 months from study entry by research staff at recruiting sites, based on electronic or paper case notes, via the CRF.

- Invasive fungal infection (IFI) treatment outcome: Data on the outcome of IFI treatment will be collected during the last follow up assessment (12 months post randomisation). These will be categorised as: treatment given and completed with no relapse; treatment given and completed, but with relapse; ongoing treatment; and IFI related mortality.

- Antifungal associated adverse effects/events/complications: These will be collected via the adverse event reporting procedure (Section 13) and/or from relevant follow up CRFs as appropriate. Collected throughout the 12-month period following randomisation.

- Resource use: Data on resource use will be collected to inform the economic evaluation. This will include hospital care health service use (e.g. length of hospital inpatient stay, readmissions and outpatient visits) and product costs. These data will be collected from hospital records on a monthly basis.

- Episodes of neutropenic fever requiring hospital admission or outpatient management: Episodes of neutropenic fever will be assessed using the standard ESMO Clinical Practice Guidelines definition [2]. Where these require hospital admission, this will be recorded in relevant CRFs throughout the patient follow up period.

- Antifungal resistance in fungi (non-invasive and invasive): isolated from clinical specimens taken as part of routine care (i.e. additional samples will not be taken unless the patient has consented and the site is participating in additional sampling for storage/research). This will be reported to YTU for the 12 months from study entry by research staff at recruiting sites, based on electronic or paper case notes, and when required microbiology results systems, via the CRF.
- Desirability of Outcome Ranking (DOOR) [3]: by defined hierarchical levels to be developed and confirmed following discussion with stakeholders, using Delphi methodology [4], and our Patient Advisory Group. Data used for this will be collected throughout the 12 month follow up period. 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.

Follow up will be for 12 months from trial entry. This encompasses the time for induction/consolidation chemotherapy and neutrophil recovery. The risk of IFI is correlated with prolonged neutropenia so follow-up beyond 12 months is not required to capture necessary outcomes. Patients will be reviewed monthly for data collection relating to outcomes.

### 6.3 Internal pilot and recruitment rates

An internal pilot phase will run during the first 9 months from the start of recruitment. This period will be used to assess recruitment and retention rates, and intervention fidelity, and provide guidance on optimising the trial processes. The BioDriveAFS trial will integrate a mixed methods process evaluation in parallel to the internal pilot and full trial, which is detailed in Section 7. This will focus on fidelity to the clinical pathway and barriers and facilitators to site trial participation and implementation.

The proposed recruitment rate is based on a recruitment period of 30 months with 21 sites in total, to recruit 404 participants.

# 7 MIXED METHODS PROCESS EVALUATION

## 7.1 Aims

The overall aim of the process evaluation is to robustly evaluate how the intervention is delivered during the internal pilot and main trial.

Specific aims are:

1. To understand in which contexts/settings the intervention works better, and why (qualitative)
2. To explore implementation barriers/facilitators to inform post-trial implementation (qualitative)
3. To assess fidelity to the clinical pathway (quantitative and qualitative)

## 7.2 Process evaluation overview

Process evaluations within trials explore the: (1) implementation; (2) receipt; and (3) setting of an intervention and help in the interpretation of the outcome of results [43]. This can help improve the validity of the intervention findings alongside helping to explain specific reasons why an intervention succeeded or failed [44]. A process evaluation often answers the question ‘where does the intervention work, how and why?’ A key component of a process evaluation is that of implementation ‘fidelity’ which measures the degree to which an intervention was implemented as intended [45].

Biomarker based antifungal stewardship (BBAFS) is a complex intervention [46] and as such it is possible that trial outcomes will reflect variation in delivery rather than the intervention’s design. Interpreting trial outcomes therefore requires close attention to what is delivered. Information on the underlying mechanisms of action and contextual factors that shape the delivery and use of BBAFS, will also be important for its optimisation after trial completion and for replicating any success that occurs in future delivery settings.

### *7.2.1 Process evaluation timescales*

Quantitative fidelity data will be collected continuously across all wards and from all intervention arm patients, from month 1 to month 36 by site research nurses.

As the trial recruitment period is 30 months in duration, continuous qualitative data collection across this entire time period would be impractical and quite likely go beyond saturation. Therefore, the two main periods of qualitative data collection will be: months 1 to 9 of recruitment (first phase, covering the pilot study) and then months ~25 to ~32 (second phase, covering the latter part of the main trial). The selection of months 25 to 32 is to allow for the intervention to become normalised into the settings by that time point but also to allow time for qualitative findings to be analysed before the end of the trial follow up period.

See Table 1 for more detail on the process evaluation timescales.

**Table 1:** *Process evaluation timescales*

| | Months of trial | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pilot phase | | | Full trial | | | | | |
| | 1-3 | 4-6 | 7-9 | 10-12 | 13-24 | 25-27 | 28-30 | 31-33 | 34-38 |
| Quantitative fidelity assessment data collection | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| Per pathway step assessment | ■ | ■ | ■ | | | | | | |
| Qualitative data collection with healthcare staff (both declining and participating sites) | ■ | ■ | ■ | | | ■ | ■ | ■ | |
| Qualitative data collection with patients | ■ | ■ | ■ | | | ■ | ■ | ■ | |
| Qualitative analysis of Site Initiation Videos (SIVs) | | | ■ | ■ | | | | | |
| Qualitative analysis of Site Antifungal Policies | | | ■ | ■ | | | | | |
| Interim quantitative analysis of adherence | | | | ■ | | | | | |
| Interim qualitative analysis of implementation | | | | ■ | | | | | |
| Integration of above to make refinements | | | | ■ | | | | | |
| CFIR implementation analysis | | | | | | | | ■ | ■ |
| Definitive inductive qualitative analysis | | | | | | | | ■ | ■ |
| Development of moderating factors | | | | | | | | ■ | ■ |
| Definitive quantitative fidelity assessment | | | | | | | | | ■ |
| Interviews with highest and lowest ranked sites | | | | | | | | | ■ |

### *7.2.2 Process evaluation sampling*

Quantitative fidelity assessment: data collected about all intervention arm patients (n≅200).

Qualitative context, implementation and fidelity evaluation: purposive sampling of **eight participating sites** chosen on size, hospital type (transplant vs non transplant), geographical location and AML/HRMDS/ALL/tMPN patient throughput.
Purposive sampling of **eight to ten declining sites** chosen on diversity of decline decision and reasons for declining (e.g., due to lack of capacity or their antifungal policy).
Analysis of all Pre-SIV and SIV videos and site antifungal policies to understand decisions behind sites participating or declining to participate in the trial.

## 7.3 Quantitative – assessment of fidelity to the clinical pathway

Quantitative measurement will focus on the core principles of adherence, defined as:

- *Content:* did the clinical team deliver the intervention as designed by the research team?
- *Frequency and duration:* did the clinical team deliver the intervention as often and as long as planned, based on pre-specified targets?
- *Coverage:* was the intervention delivered to all eligible participants?

Assessment criteria

- Did participants undergo GM/BG testing as per the care pathway? (Yes or No) If no, why? Information to be included on frequency of biomarker testing and, where applicable, duration
- Was the care pathway modified/adapted at any sites? (Yes or No) If yes, why and in what ways? At which sites?
- Did participants receive AF when not indicated by the care pathway? (Yes and No) If yes, why?
- Were all eligible patients on the ward invited to participate in the trial? If no, why not?

Sample

Data collected for every intervention patient enrolled in both the pilot and main trial, across all sites. See sections 11.6 to 11.8.

Procedure

Local research nurses at each site will collect the above data for each patient. Informed consent for this data collection will be taken from patients when they consent to take part in the trial. The information the research nurses needs to collect will be embedded as questions within the Case Report Form, per patient. The majority of information the research nurse needs to complete the process evaluation CRF questions will be retrospective and the data will be contained within the patient's medical notes, leading to minimal patient burden. Occasionally, the answers to the CRF questions may not be fully covered within medical notes. For instance, a research nurse may be able to see that a patient was given AF treatment whilst they were enrolled in the trial and the reason why is not obviously recorded. In this instance, the research nurse would ask the patient's lead clinician (verbally or via phone or email) for a brief insights into why that clinical decision was made in order to better inform the fidelity assessment.

In the pilot stage, we will additionally conduct a more granular, 'per pathway step' assessment. Site research nurses will record Yes/No for each *defined treatment step* of the pathway, with a reason attributed for each intervention arm patient (See Flow Charts in Section 3 for each treatment step of the pathway). This phase may involve more intensive work for research nurses to chase up the reasons with lead clinicians as to why specific parts of the pathway may not have been followed.

Fidelity scoring

We will develop an intervention fidelity scoring matrix, based on existing guidance [45]. Towards the end of the study, an aggregate score will be produced which will be taken from all three fidelity domains (content, frequency and duration, coverage). Adherence will be categorised on a scale of 0-3 for each of the sites, with 0 representing no adherence, 1 representing some adherence, 2 representing mostly adhering and 3 representing full adherence. All 21 sites will be given an overall fidelity score and ranked accordingly. For the five sites that rank highest and the five sites that rank lowest, the lead clinician for the site will be interviewed over the phone to understand site level fidelity (see Section 7.4 for more detail).

### 7.4 Qualitative – understanding context and exploring implementation

At eight selected sites, both patients and healthcare staff will take part in qualitative research during the internal pilot study and also later in the main trial. This will predominantly take the form of focused interviewing although some healthcare staff may opt to take part in a focus group. Interviews will be conducted with lead clinicians at eight to ten sites that declined to participate in the trial, alongside

analysis of Pre-site Initiation Visit (Pre-SIV) meetings, Site Initiation Visit (SIV) meetings and antifungal policies documents of all sites to better understand the levers for sites accepting and declining being involved in the trial.

The primary goal of the qualitative work is to understand 'what works, for whom, when and why?' alongside implementation barriers and levers. We will capture site based contextual factors that may shape the way the intervention is implemented and delivered, as well as why some sites have declined or accepted to take part at the pilot stage.

*7.4.1 Interviews*

Sampling:
*Healthcare staff:* Approximately five 'key informants' at each of the eight sites per phase (40 participants x2 timepoints). Interviews are likely to be a mixture of face to face, video or phone. Participants will be healthcare professionals who are key implementers of the intervention and those who provide clinical care for this patient group such as: haematologists, infection doctors, pharmacists, nurses and allied health professionals.
Importantly, this will also include the lead research nurse for the site who has recruited patients to the trial. We would expect a level continuity of healthcare staff participants between timepoint 1 (months 1-9 from start of recruitment) and timepoint 2 (months ~25 to ~32) but are realistic that staff often move around the NHS and new participants may come on board at timepoint 2. See Section 7.2.1 for more details on timescales.

*Patients:* Phone or video interviews with a purposive sample of 40 patients overall (20 patients x2 timepoints) who have been discharged from hospital having been recruited to the intervention arm of the trial whilst they were an inpatient. Participants will be sampled on: age, gender, ethnicity and length of hospital stay. The researcher will speak to between one and three patients per site based on site size and recruitment numbers. Patient participants will be 40 unique individuals – patients will not be interviewed twice.

*Lead clinician per site:* Towards the end of the study, after all 21 participating sites have been ranked on quantitative fidelity data, the lead clinician for the study at the five least adherent sites and the five highest adherent sites will be asked to take part in a one off phone interview.

*Declining sites clinical leads:* Brief focused telephone interviews with a clinical lead that has been in communication with YTU from around 8 to 10 declining sites. This will be a one-off phone interview taking place at time point 1 (the pilot phase). Multiple sites declined to take part in the trial in response to email invitations by the research team. The rationale behind these interviews is to provide more nuanced understandings of why sites may decline and equally what the levers for acceptance are as BioDriveAFS ultimately requires 21 sites to host the trial.

Interview conduct:
*Healthcare staff:* A mixture of interviews and focus groups dependent on participant preference. Participants will be asked to talk in a non-identifying manner about a patient who was randomised to the intervention and a patient who was randomised to the control, to ground the interview/focus group. Questioning will predominantly focus on the practicalities of the intervention, problems and successes, systems/relationships/site set-up, which may influence uptake of the intervention, opinions about using the intervention with this patient group, and any changes in practice occurring with control group

patients. We will also aim to generate an understanding of the main moderating factors influencing intervention fidelity.
The interview or focus group is likely to last around 30 to 40 minutes. A portion of the topic guide will likely be based on the core constructs of Normalisation Process Theory [47].

*Patients:* The purpose is to understand patients' perceptions of the intervention and questioning will be participant led. The interview is likely to be grounded in participant's understandings and experience of their hospital treatment and knowledge/ perceptions about the intervention they received. Example topics might relate to: being an AML/HRMDS/ALL/tMPN inpatient, knowledge of fungal infections and their treatment (and experience of this), how the intervention was delivered and how patients felt about being in receipt of it, how parts of it could be optimised. The interview is likely to last between 40 – 60 minutes. The topic guide will be developed with PPI input. All interviews for both participant groups will be audio recorded and transcribed.

*Lead clinician per site:* This will take the form of a brief, structured telephone interview lasting around 20 minutes. Questioning will be based on the moderating factors developed via the staff and patient interviews, although lead clinician's own thoughts as to why the intervention may have succeeded well or less well at their site will be encouraged. We will also ask lead clinicians briefly at the start of the interview why their site agreed to take part in the trial.

*Declining sites clinical leads:* This will also take the form of a brief, structured telephone interview lasting around 20 minutes. The interview questions will explore reasons for declining. Some interviews may be straightforward in regards to reasons for declining (e.g., a lack of capacity amongst the clinical and/or research nurse team), whereas others may be more nuanced and explorative (e.g., where the decline reason is due to their current antifungal policies or particular clinicians not being on board).

<u>Approach and consent process:</u>

*Healthcare staff:* Researchers will approach healthcare staff to invite them to take part in interviews or a focus group. This initial approach will be via email or a short verbal description about what participation in the research involves. Identification of healthcare staff for interview is likely to be via the research nurses at each site. If healthcare staff indicate that they are interested in being interviewed they will be given an information sheet and opportunity to ask questions. Healthcare staff members that agree to participate will be emailed a consent form. Prior to a phone or video interview beginning, the researcher will ask for participant's verbal consent to each item on the written consent form. Taking of this verbal consent will be audio recorded.

*Patients:* Research nurses in collaboration with the process evaluation researcher will identify trial participants - whilst they are in hospital receiving treatment - who may be interested in taking part in a phone or video interview about the intervention once they have been discharged from hospital. The research nurse will ask for permission from the patient for their contact details to be forwarded to the process evaluation researcher. One to two weeks after the patient has been discharged, the researcher will phone the patient and gauge whether they may be interested in being interviewed. If the patient is interested, they will be posted or emailed a participant information sheet and a consent form for them to read prior to the interview taking place. Where the research nurse feels it appropriate, the participant information sheet and informed consent form for interviews can be provided to the patient for consideration whilst still in hospital during consent for the main trial. Prior to a phone or video interview beginning, the researcher will ask for participant's verbal consent to each item on the written consent form. Taking of this verbal consent will be audio recorded. The process evaluation

lead has successfully tried and tested this method of gaining verbal consent across several different qualitative studies recently ([48]; ESRC Funded project [ref. ES/W001810/1]). Participants will be reassured that their involvement is entirely voluntary, the interview can stop at any time and any withdrawal from the process evaluation will not affect their future medical care in any way. A criteria for taking part in this interview is that the participant must have mental capacity to independently consent. Language and literacy considerations will be the same as entry to the trial itself.

*Lead clinician per site:* Approach and consent process will be the same as detailed in the "healthcare staff" section above.

*Declining sites clinical leads:* As with the healthcare staff participants, researchers will invite clinical leads to take part in the interview. This initial approach will be via email or a short verbal description about what participation in the research involves. Identification of interviewees will be via the recruiting YTU research team and co-Chief Investigators. If clinical leads indicate that they are interested in being interviewed they will be given an information sheet and opportunity to ask questions. Those that agree to participate will be emailed a consent form. Prior to a phone or video interview beginning, the researcher will ask for participant's verbal consent to each item on the written consent form. Taking of this verbal consent will be audio recorded. We will also explain that we respect their informed decision to decline involvement in the trial and that the interview does not aim to challenge or change this decision, rather it aims to capture a better understanding of reasons behind declining.

*7.4.2. Analysis of SIV videos*

Sampling:

*Analysing recordings of SIV meetings:* As part of the pilot phase, YTU staff have been conducting site initiation visits (SIV) when a site indicates it is ready to go ahead with the trial. A precursor to an SIV is a preliminary meeting between YTU and a clinical team called a "pre-SIV". All pre-SIVs and SIVs have been conducted over video call and have been recorded as standard practice. Most of the pre-SIVs and SIVs hold a wealth of information about a site's attitude and ethos towards the trial and intervention. Some pre-SIV meetings have been held with sites who have subsequently declined to take part in the trial, giving YTU staff a great understanding of why a clinical team may decline to take part. We will include the recordings of the pre-SIV and SIV meetings as part of the process evaluation analysis. Again, this will help provide an understanding of the levers of accepting and declining site participation in the trial as well as the context in which the trial will be situated for each site. The sample for inclusion of all pre-SIV and SIV videos is all sites both past and future who take part in one of these meetings as part of the trial set up.

Approach and consent process:

*Analysing recording of SIV meetings:* Each member of a clinical team who appears in a recorded video will be emailed and asked for their consent to include the recorded meeting conversation in the process evaluation analysis (with an explanation of why we want to do this in the email alongside a detailed 'further information' or participant information document). If they decline, we will not include their contribution to the conversation in the analysis. If we receive no email response, we will send 2 further reminder emails. After these 2 reminder emails giving them the option to opt out, if there is still no response we will proceed to include their contribution in the analysis. They will be clearly made

aware of this in the emails. There is no reference to individual patients or instances of individual care provision in these recordings.

### 7.5 Descriptive data

The process evaluation team will collect descriptive detail through desk-based work, which will consist of:

- Data about key ward characteristics, collected in the form of a log by research nurses for each of the 21 sites. Data will likely consist of hospital size/type, AML/HRMDS/ALL/tMPN patient throughput, geographical location, length of stay and any other important data. This data log will assist in the sampling of the eight sites for the qualitative work.

- Recording of tacit knowledge about the eight sites involved in the qualitative work. We will aim to capture informal/ tacit knowledge which is of interest to understanding context, implementation or fidelity. By tacit knowledge, we mean data that is useful to the process evaluation but which exists outside of the formal interviews, such as opportune phone calls, emails or face to face information collected during site visits. Recording of such knowledge will be done via the form of field notes and a researcher reflections diary. An example of how this data might be important is to understand the differing levels of site engagement in the set up period of the trial.

- We will obtain antifungal policies from sites that have both accepted and declined to take part in the trial as the differing antifungal policies between sites may be driving variation of participation. A documentary analysis will be conducted of antifungal policies to enable us to understand the diverse approach to antifungal treatment for patients, differences and similarities and whether antifungal policies for haematology patients at some sites are too prohibitive for clinical teams to take part in the trial. Antifungal policies will be collected from accepting and declining sites by emailing site personnel who have been in contact with the YTU team during the pilot phase, asking whether they are willing to send their policy documents. They will be informed of these forming a documentary analysis. The documents are likely not to be in the public domain, therefore we will ask for email consent statements from each site contact to include them in the analysis. This will be requested via email alongside an email explanation about why we want to carry out a documentary analysis.

**Table 2:** *Data collection methods, sample and time points*

| **Component of process evaluation** | **Method** | **Participant** | **Sample size** | **Time point** |
|---|---|---|---|---|
| Data about ward characteristics | Completion of baseline data log | Research nurses | One log per participating ward | During study set up at each site |
| Fidelity assessment<br>(quantitative) | Data collected from patients' medical notes | Patients (no contact) | All intervention arm patients | Pilot and main trial |
| Understanding context and exploring implementation (qualitative) | Interviews or focus groups | Healthcare staff | 80 overall<br>40 participants x2 (does not have to be same participants) | 40 during pilot trial<br>40 during main trial |
| Understanding context and exploring implementation (qualitative) | Interviews | Patients | 40 overall<br>20 participants x2 (does not have to be same participants) | 20 during pilot trial<br>20 during main trial |
| Understanding context (qualitative) | Interviews and SIV recordings | Clinical leads of declining sites and all pre-SIV and SIV videos | 8-10 sites overall (8-10 clinical leads)<br>SIV recordings of as many sites as relevant | Interviews during pilot trial<br>SIV recordings analysis during months 7-9 of pilot phase and months 10-12 of full trial |
| Fidelity assessment<br>(qualitative) | Structured phone interviews | Lead clinician per site | 10 sites overall<br>5 highest performing sites<br>5 lowest performing sites | Towards end of trial |
| Recording of tacit knowledge | Field notes | By proxy from healthcare staff and research nurses | As many sites as relevant | Set up, pilot and main trial |
| Antifungal policies documentary analysis (descriptive qualitative data) | Documentary analysis | Antifungal policies from both accepting and declining sites | As many sites as relevant (both declining and accepting sites) | During months 7-9 of pilot phase and months 10-12 of full trial |

## 7.6 Analysis

Qualitative data will take the form of interview transcripts and quantitative data will take the form of information collected from patient clinical records. Analysis of these data will be performed in three phases; 1) after the pilot phase of the trial (months 1 to 9 of recruitment); 2) towards the end of the recruitment period (within the last 6 months of recruitment); and 3) towards the end of the trial. Further details are shown in Table 1 (Section 7.2.1).

After the first phase (pilot phase):

Quantitative: A basic descriptive statistical analysis paying attention to interim levels of adherence – and where adherence differs between sites - based on the quantitative data collected during the pilot. For a description of the quantitative summaries that will be used to report on adherence data, please see Section 14.4.

Qualitative: A rapid descriptive, thematic analysis to generate headline themes exploring levers for accepting or declining participation in the trial, commonality and differences across sites about context, clinical systems, team set-up/relationships and emerging important factors regarding implementation. Interim moderating factors will be identified.

Mixed methods integration of the above quantitative and qualitative analyses to make refinements to the treatment pathway/clinician training to improve adherence moving forward into the main trial.

After the second phase (towards the end of recruitment):

Qualitative x2: 1) A deductive analysis of data from both phases using the Consolidated Framework for Implementation Research (CFIR) [49] to understand core implementation barriers and levers. All CFIR domains will be included (intervention characteristics, outer setting, inner setting, characteristics of individuals, process of implementation). The purpose is to develop a robust post-trial implementation strategy and package which will encourage a ‘soft landing’ of the intervention (should it prove successful) in the wider NHS. 2) A second rapid, inductive descriptive analysis (building on the first undertaken after the pilot phase) with two purposes a) a focus on whether the intervention is becoming normalised in the settings, or not, and how/why b) generation of definitive moderating factors (e.g. intervention complexity, facilitation strategies, quality of delivery, and participant responsiveness) which may explain low or high fidelity at sites.

Towards the end of the trial period:

Quantitative x2: 1) Analysis of the quantitative fidelity data for the main trial, using descriptive statistics (see Section 14.4) 2) Fidelity assessment using a fidelity scoring matrix (details given of scoring matrix in Section 7.3)

Qualitative x2: 1) Deductive qualitative analysis of phone interviews with the x5 highest and x5 lowest ranked sites regarding fidelity. Framework analysis of responses. A dynamic logic model [50] will be developed to explicate the theory of change of the intervention following its testing in the trial.

### 7.7 Data transfer and storage

All process evaluation data will be analysed and stored at the University of York (UoY). Audio data will be removed from recording devices as soon as is practicable and will be transferred and stored on secure, password protected servers at UoY. Audio files will be transcribed in house by a trained typist who works as an administrator at UoY. The files will be accessed via the secure, password protected servers at UoY. A confidentiality and data security agreement is already in place. Only the research team members will have access to data. Separate verbal consent audio recordings will be stored for 5 years, after which these electronic data will be deleted. Interview audio recordings will be deleted as soon as possible following transcription. Interview transcripts and any paper data will be stored for a period of 10 years, when paper data, confidential waste and electronic data no longer required for analysis will be disposed of / deleted.

## 8 TRIAL SETTING

The trial will take place at multiple NHS haematology departments (≅ 21 centres) responsible for the care of AML/ALL/HRMDS/tMPN patients over a 2.5 year trial period. The trial will be conducted in haematology units delivering chemotherapy in line with national guidance. Sites must also be able to currently or ascertain access to GM *and* BG testing either internally or externally.

## 9 TRIAL INTERVENTIONS/ARMS

### 9.1 Biomarker-driven approach (intervention arm)

Patients will have twice weekly blood tests for GM and BG from the start of treatment until at least 7 days after neutrophil recovery, defined as per usual local cut-off / clinical practice, with each cycle of chemotherapy. Patients spend a high proportion of their time as inpatients during this period, but during periods of lower risk (as deemed by the clinical care team), when the patient is being seen via outpatient clinics, testing can be reduced to once weekly or as often as the patient is attending (but no more than twice weekly) [i.e. patients do not require additional outpatient clinic appointments above what is the normal standard of care to participate in this trial].

For patients treated with a targeted agent such as venetoclax, ivosidenib or gilteritinib which is given continuously until disease progression or toxicity then biomarker monitoring should be continued for a minimum of three months. After three months of monitoring of patients treated with targeted agents biomarker monitoring should be continued for as long as local standard of care antifungal prophylaxis would be continued (i.e. if after 3 months antifungal prophylaxis is usually discontinued locally with ongoing use of targeted agents then biomarker monitoring can also be discontinued; if ongoing antifungal prophylaxis is usually prescribed after 3 months then biomarker monitoring (at least once weekly) should be continued).

A clinical pathway approach (see intervention flow chart, Section 3.2), with integration of existing guidelines and definitions will guide the prevention, investigation, and therapy of IFI [16, 17, 22, 51]. Whether symptoms are present or not, patients with two positive tests (either GM and BG both positive or GM or BG positive on consecutive occasions) will be recommended for an urgent high-resolution CT (HRCT) scan of the lungs (<=24 hours or ASAP thereafter) and, if indicated, of other body sites. A bronchoscopy and AF therapy will be recommended if there are radiological features of IFI in line with guidance and, for centres with access to it, GM BAL is recommended (not mandatory) [16, 22, 51]. If

the patient meets the criteria, based on testing, of proven/probable IFI then targeted AF therapy according to the site's, or national/international, guidelines, at the discretion of the patient's clinical team, will be recommended.

HRCT (± BAL), or other directed tests in line with guidance [16, 22], will also be recommended for patients with neutropenic fever ≥96 hours or other symptoms suggestive of IFI, but AF will be discouraged if GM and BG remain negative in the absence of other evidence of IFI (proven/probable)[17]. In the survey performed during trial design with key stakeholders and service providers, the most used test for the investigation of IFI in an AML patient with prolonged NF was HRCT (75%) followed by GM (69%), BG (61%), BAL (58%) and then BAL GM (44%); these have all been incorporated into our care pathway.

In the event that a performed biomarker test fails due to technical or other reasons, the site team will repeat the test as soon as it is practically possible to do so.

*The clinical team will always retain the right to deviate from the pathway.* When this occurs, it will need to be documented within the CRF by site research teams. See the study flowcharts (Section 3) for the recommended clinical care pathways. Additional biomarkers (e.g. Candida or Aspergillus PCR) *cannot* be used as regular IFI surveillance tools (as GM or BG are being used), but can be used 'reactively' at the clinical care team's discretion during episodes of prolonged NF or when the patient exhibits other symptoms/signs of IFI (as is the case in the control/SoC arm; see Section 9.2 below).

### 9.2 Prophylactic antifungals and standard of care approach (control arm)

Patients will receive prophylactic AF in keeping with guidelines [52]. As a minimum, prophylaxis should be given for the duration of chemotherapy-related neutropenia, at least until neutrophil recovery ( >0.5 x $10^9$/L). Prophylaxis can be given either with each cycle of chemotherapy, or throughout and between subsequent cycles of chemotherapy, as per the usual standard practice at the local study site. We are aware some sites stop AF prophylaxis at neutrophil recovery between cycles of chemotherapy – this is acceptable if it is the usual practice at the study site.

For patients treated with a targeted agent such as venetoclax, ivosidenib or gilteritinib which is given continuously until disease progression or toxicity then local standard of care antifungal prophylaxis should be continued for a minimum of three months. After three months, further antifungal prophylaxis should be given in line with the usual local standard of care.

Monitoring (regular testing) with GM or BG while the patient is stable (i.e. does not have NF or illness) will not be used in this arm. Patients with persistent NF ≥96 hours or other symptoms suggestive of IFI will be investigated and managed according to existing local SoC (non-culture-based [biomarker] tests allowed when used in a 'reactive' manner). Participants in this arm must receive prophylactic AF therapy with a recognised anti-Aspergillus agent (Posaconazole [used by 66% in our survey], itraconazole [only when one of the other azoles cannot be used], isavuconazole, voriconazole, liposomal amphotericin, or [when azoles cannot be used] anidulafungin, caspofungin or micafungin). Fluconazole *cannot* be used as the prophylactic agent.

### 9.3 Adherence with the intervention

Wherever possible, participants should remain in their allocated treatment arm for the duration of their 12 month follow up period (or until they die/withdraw from follow up), unless there is a compelling medical cause to deviate from this. For example, if a participant were to have a relapse of their disease during the 12 month period and start a new course of treatment, they should continue

receiving the treatment intended for their allocated trial arm (intervention/control); this should not be a cause to cease or change treatment.

Reasons for participation or non-participation of sites in the trial and participating sites' adherence with the two arms of the study will be assessed qualitatively as part of the process evaluation (see Section 7) during the internal pilot phase and quantitatively via the data collected by local site research teams in the CRF. It is important that site research teams put in place local mechanisms that ensure the twice weekly biomarkers (GM and BG) are performed, and results acted upon, in patients randomised to the intervention arm of the study. This is likely to be particularly important at sites that currently perform limited or no biomarker monitoring or reactive testing.

We are also aware that GM and BG turnaround time can be variable, but as this trial is pragmatic and has been deliberately designed within the context of existing NHS resources and laboratory frameworks, a particular length of turnaround time does not preclude participation in the trial. Nevertheless, we strongly encourage site primary investigators to establish and discuss local turnaround times with laboratory leads to assess whether simple improvement measures (without additional cost to the trial) can be put in place, such as the research nurses taking samples directly to the laboratory or sending samples externally directly from the ward or clinic setting. An educational intervention regarding turnaround time and how to improve it is being developed and will be shared with sites.

# 10 PARTICIPANTS

Patients who have a diagnosis or relapse of acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), high-risk myelodysplasic syndrome (HRMDS) or AML transformation of a myeloproliferative neoplasm (tMPN), who need chemotherapy ('intensive' or 'non-intensive' regimens which cause chemotherapy-related prolonged neutropenia, mandating *antifungal prophylaxis and/or systematic IFI biomarker monitoring)* and who meet all eligibility criteria detailed in Section 10.1 and 10.2 will be included.

Patients will be identified at the point of diagnosis in outpatient clinics and wards of haematology departments of participating NHS hospitals prior to chemotherapy and not when the patient is ill with *prolonged* (> 72 hours) neutropenic fever. Further details of the methods for eligibility screening and patient approach are given in Section 11.1.

## 10.1 Inclusion criteria

To be eligible for the trial patients must meet all of the following criteria:

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

## 10.2 Exclusion criteria

Patients will be excluded from study entry if any of the following apply:

1) Previous proven or probable *invasive* fungal infection (IFI) (according to the EORTC/MSG criteria [17]). *(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

# 11 TRIAL PROCEDURES

## 11.1 Patient identification and screening for eligibility

Potentially eligible patients will be identified by local trial teams and clinicians at diagnosis either in the outpatient clinic or as inpatients within participating NHS haematology departments responsible for the delivery of chemotherapy to AML/ALL/HRMDS/tMPN patients. All patients (≥16 years old) with AML/ALL/HRMDS/tMPN embarking on treatment at trial sites will be screened for eligibility. To ensure diversity of participation, we will collect data at screening/randomisation about patient characteristics that could potentially impact trial endpoints such as age, postcode (to calculate index of multiple deprivation score (IMD), only first half of postcode collected for non-randomised patients), ethnicity, and sex, which will be monitored by the Trial Management Group (TMG).

The central research team will work closely with the treating clinicians and local research teams at each participating site via engagement, training and networking to optimise the local screening and recruitment processes, initially at the point of site set-up and initiation. Thereafter, there will be various opportunities to adapt and optimise this further; including at planned site training events, through real-time site networking (e.g. via the BSAC E-Forum that will be set-up to share experiences, etc.), based on advice from PPI meetings and learnings from the pilot phase process evaluation work (see Section 7).

## 11.2 Informed consent

Patients will be provided with a paper or electronic patient information leaflet (PIL). For patients unable to read, narrated versions or voice-assisted software will be used depending on local NHS availability given patients will be recruited in hospital settings. For those unable to speak English, we will use either a translator or language line depending on local availability. Patients will have the opportunity to ask questions of the recruiting research team (i.e. research medic or nurse) and given as much time as they need, prior to commencing chemotherapy, to decide before completing consent processes, within the time constraints of clinical decisions with regards to beginning their treatment. Consent will be recorded via paper consent forms, which will be uploaded onto the secure web-based data collection interface ‘REDCap’ once complete, or via participant e-consent directly within the REDCap system.

Informed consent will be obtained by a suitably qualified and experienced local research nurse or clinician who has been authorised to do so by the Chief or Principal Investigator, as detailed on the study Delegation of Authority and Signature Log for the study site.

The original signed form will be retained at the study site within the Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants, retained in the participant medical notes, and provided to York Trials Unit. Record of e-consent will be emailed to the participant and site for filing (where no participant email address is provided, a copy will be printed and provided to participants).

The PIL will include an infographic, developed with our Patient Advisory Group (PAG) that explains the trial visually and in an accessible manner including the potential benefits and risks of participating. All information required by the UK Health Research Authority will be included. Throughout the whole study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion.

For study sites participating in the parallel studies (see Section 12), consent will also be sought from patients for the taking of additional and/or left-over samples for storage and research (this is not mandatory for participation by the site or patient), and for participants to be contacted again in the future for the purposes of further research, where not already outlined in the trial consent form, relating to these samples (this is not mandatory for participation by the patient). Full details of this component of the trial will be explained to the patient in the relevant PIL where it will clearly state that consent to this component will not affect inclusion in the main trial.

## 11.3 Patient incentives

Participants will be given an unconditional £10 voucher as a goodwill gesture with each follow-up questionnaire (at three, six and 12 months).

The nature of the trial is that we intend to align interventions with inpatient care and regular hospital visits, which are usually at least once or twice weekly for most acute leukaemia patients so travel to hospital for the purposes of the trial is not anticipated. Likewise, follow-up assessments (e.g. EQ-5D-5L) will be completed online, over the phone or by post as appropriate/required.

## 11.4 Randomisation

Once participant eligibility has been confirmed and consent has been completed (as per Section 11.2), randomisation will be undertaken using REDCap. The system will perform independent randomisation 1:1 (Intervention : Control), using block randomisation stratified by site, with randomly permuted block sizes. All baseline data (see Section 11.7) should be collected prior to randomisation wherever possible but objective measures (e.g. baseline comorbidities) may be completed afterwards as soon as possible following randomisation. The patient completed EQ-5D-5L must be collected prior to randomisation to minimise potential risk of bias from knowledge of treatment allocation.

### *11.4.1 Allocation concealment and blinding*

The allocation schedule will be generated by a statistician not involved in recruitment. As this is an unblinded trial, patients and treating clinicians will be informed of the allocation. Local research teams will be asked to place the allocated patient pathway in the patient's hard copy and/or electronic case records so clinical teams have access and can refer to the document.

## 11.5 Definitions of invasive fungal infection (IFI)

For a patient within the trial to be defined as having probable IFI they must have at least one clinical feature *plus* mycological evidence as detailed below in Table 3 (all patients, by definition, will have at least one host factor), based on the definitions from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) [17]. Please note that for the purposes of the proposed care pathway in the intervention (biomarker) arm, the cut-offs to trigger further investigation for IFI when the patient does not have NF are any value above the upper limit of the normal range for the test (GM or BG) being used. For the purposes of diagnosis for the endpoints of the trial and where it states "probable/proven IFI" in the proposed care pathway, the cut-offs below will be used. The definitions for diagnosis of IFI will be the same for both arms of this trial. Patients

that do not fit the EORTC/MSG definition of possible infection but who have persistently unexplained positive biomarkers (both or the same single biomarker consecutively), and are remaining to be or are progressively unwell, should be managed as a possible IFI in terms of considering therapeutic antifungals (see intervention flow chart in Section 3.2 for detail).

**Table 3:** *Definitions for diagnosis of Invasive Fungal Infection (IFI) [17]*

<table>
<tr><th>Fungi</th><th>Proven</th><th>Probable</th><th>Possible</th></tr>
<tr><td rowspan="2">Moulds</td><td rowspan="2">● Sterile specimen demonstrating tissue invasion with hyphae or melanised yeast-like forms<br>● Culture from sterile site, with associated clinical or radiological evidence of disease (excl. BAL, paranasal sinus, mastoid sinus, urine)<br>● Growth from Blood culture<br>● PCR from fixed tissue specimen</td><td>Requires 1 each of Host factor, Clinical Feature, and Mycological evidence</td><td>Requires 1 Host Factor, and 1 Clinical Feature</td></tr>
<tr><td colspan="2">Host factors:<br>● Recent neutropenia (<0.5 x$10^9$/L) for >10 days<br>● Active haematological malignancy<br>● Previous allogenic Stem Cell or Solid organ Transplant<br>● ≥0.3mg/kg prednisolone equivalent for ≥3 weeks (past 60 days)<br>● T-cell immunosuppression (last 90 days)<br>● B-cell immunosuppression<br>● Inherited severe immunodeficiency<br>● Acute GVHD grade III/IV involving gut, lung, liver refractory to first-line steroids<br><br>Clinical features:<br>● Pulmonary Aspergillosis - Dense, well-circumscribed lesion(s) +/- halo sign; Air-crescent sign; Cavity; or Wedge-shaped and segmental or lobar consolidation<br>● Other Pulmonary moulds - as above, or reverse-halo sign<br>● Tracheobronchitis - Tracheobronchial ulceration; nodule; pseudo-membrane; plaque; or eschar<br>● Sino-nasal disease - Acute localised pain, Nasal ulcer with black eschar, and extension across bony barriers<br>● CNS - Focal lesions or Meningeal enhancement on MRI/CT</td></tr>
</table>

| | | |
|---|---|---|
| | | ***Mycological evidence:***<br>● Microscopic detection of fungal elements in sputum, BAL, bronchial brushings or aspirate<br>● Mould recovered by culture from sputum, BAL, bronchial brushings or aspirate<br>● GM - Single serum or plasma, BAL fluid or CSF ≥1.0; or serum or plasma ≥0.7 AND BAL fluid ≥0.8<br>● BG ≥80ng/L in 2 consecutive serum samples with exclusion of other aetiology<br>● Aspergillus PCR - Blood, plasma or serum 2 consecutive positives; BAL fluid 2 positives; or blood, plasma or serum AND BAL fluid positive |
| ***Yeasts*** | ● Sterile-site specimen showing yeast cells<br>● Culture from sterile-site specimen, with clinical or radiological evidence of infectious disease<br>● Growth from blood culture<br>● Positive cryptococcal antigen from blood or CSF<br>● PCR from fixed tissue specimen | **<u>Candida</u>**<br>***Host factors:***<br>● Recent neutropenia (<0.5 x$10^9$/L) for >10 days<br>● Active haematological malignancy<br>● Previous allogenic Stem Cell or Solid organ transplant<br>● ≥0.3mg/kg prednisolone equivalent for ≥3 weeks (past 60 days)<br>● T-cell immunosuppression (last 90 days)<br>● inherited severe immunodeficiency<br>● acute GVHD grade III/IV involving gut, lung, liver refractory to first line steroids<br>***Clinical features:***<br>● Candidaemia in the past 2 weeks with 1 of:<br>● Small target-like abscesses in liver, spleen or brain, or meningeal enhancement<br>● Progressive retinal exudates or vitreal opacities<br>***Mycological evidence:***<br>● BG ≥80ng/L in 2 consecutive serum samples with exclusion of other aetiology<br>● Positive T2Candida assay |

| | | |
|---|---|---|
| | | **<u>Cryptococcus</u>**<br>***Host factors:*** (may occur in phenotypically normal patients)<br>● HIV<br>● Stem cell or solid organ transplant<br>● Haematological malignancy<br>● Antibody deficiency<br>● Immunosuppressive therapy<br>● End-stage liver or renal disease<br>● Idiopathic CD4 lymphocytopenia<br>***Clinical features:***<br>● Meningeal inflammation or consistent radiological lesion<br>***Mycological:***<br>● Recovery of Cryptococcus from any non-sterile site |
| ***PJP*** (PCP) | ● Detection of organism microscopically in tissue, BAL or expectorating sputum | ***Host factors:***<br>● CD4 count <200cells/$mm^3$<br>● Medication causing T-cell dysfunction<br>● ≥0.3 mg/kg prednisolone equivalent ≥2weeks (past 60 days)<br>● Solid organ transplant<br>***Clinical features:***<br>● Consistent radiographic features<br>● Respiratory symptoms with cough, dyspnoea and hypoxemia accompanying radiographic abnormalities<br>***Mycological:***<br>● BG ≥80 ng/L in ≥2 consecutive serum samples with exclusion of other aetiology<br>● Detection of PCP DNA by PCR in a respiratory tract specimen |

| | | |
|---|---|---|
| **Endemic Mycoses** | ● Histopathology or microscopy or specimens obtained by an affected site showing distinctive forms of the fungus<br>● Recovery of fungus from an affected site<br>● Growth from blood culture | ***Host factors:***<br>● Can occur in any patient<br>***Clinical features:***<br>● Geographical or occupational exposure with compatible clinical illness<br>***Mycological evidence:***<br>● Histoplasma or Blastomyces antigen in urine, serum or fluid<br>● Coccidioides antibody in CSF, or 2-fold rise in 2 consecutive serum samples |

### 11.6 Data collection methods

Data will be collected using bespoke case report forms (CRFs) completed electronically via the secure web-based outcome data collection interface 'REDCap', or collected on paper CRFs returned via post to York Trials Unit with data then manually entered into REDCap. All reporting of data collection will be undertaken in line with the Consolidated Standards of Reporting Trials (CONSORT) statement.

Participants will be followed up for the purposes of the study via self-completed questionnaires at three, six and 12 months. We will ask participants for full contact details at baseline (including mobile phone number, email and address) and any contact preferences. A link to complete the relevant electronic questionnaire on REDCap will be sent to participants via email, with the option to send a paper copy to participants for postal completion or completion with a researcher over the phone instead as preferred, and the option to communicate with participants via text message where appropriate (for example to coordinate questionnaire completion). Text messages are likely to be sent using secure UK-based text message gateway software such as that provided by Intelli Software (https://www.intellisoftware.co.uk).

Investigator-completed hospital CRFs must only be completed by personnel authorised to do so by the Principal Investigator, as recorded on the trial-specific delegation log for each hospital site. Investigator-completed data can be submitted at any stage during the participant's follow-up and reminders will be sent to research staff at sites to do this.

The nature of the trial is that we intend to align interventions with inpatient care, and regular hospital visits, which are usually at least once or twice weekly for most acute leukaemia patients so travel to hospital for the purposes of the trial is not anticipated. Likewise, follow-up assessments (e.g. EQ-5D-5L) will be completed over the phone or online or by post as appropriate/required.

Please see Section 7 for details of data collection for the Mixed Methods Process Evaluation, including collection of qualitative data. Please see Section 12 for a summary of the optional parallel study and the separate parallel study protocol for further details (only applicable to participating research sites).

## 11.7 Baseline assessments

The following will be collected at the baseline assessment (via methods described in Section 11.6):

- Health related quality of life: EQ-5D-5L (participant self-reported)
- Key patient demographics (e.g. age, sex, ethnicity, postcode, weight and height, employment status, living situation)
- Data relating to the patient's diagnosis (AML, ALL, HRMDS or tMPN) including baseline investigation results, planned treatment regimen and functional status at diagnosis
- Patient comorbidities and key positive microbiology results

## 11.8 Follow up assessments

### *11.8.1 Participant completed data*

The following will be collected from patients within questionnaires at 3, 6 and 12 months post randomisation. A link to complete these electronically on REDCap will be sent to patients via email/text message with alternative options available for completion via phone/post available as required/appropriate (see 11.6 for further information).

- Health related quality of life: EQ-5D-5L

### *11.8.2 Investigator (local site research team) completed data*

The following will be collected by the local site research team during the 12-month post randomisation follow up period for each participant, and will be recorded on the electronic CRF via REDCap. Investigator-completed data can be submitted at any stage during the participant's follow-up and reminders will be sent to research staff at sites to do this on a monthly basis. Due to the importance of collecting the information and reminding sites to do this regularly in the intervention arm (twice a week), more regular prompts to research teams to record biomarker tests performed may be sent.

- Prophylactic/therapeutic AF use and details (e.g. agent, dose, oral/IV, defined daily doses/full days of therapy, reason for stopping)
- Biomarker tests for IFI performed (reason for test, type, date, outcome) – see section 11.8.3 for required blood samples
- Resource use data – e.g. admissions to hospital (dates, setting, reasons, etc.)
- Episodes of neutropenic fever, associated antimicrobial use, positive microbiology, other tests
- Episodes of proven/probable IFI and non-invasive fungal infection and associated positive histological/mycological tests (including date, organism, resistance profile and susceptibilities), and other tests (e.g. high-resolution computed tomography (HRCT) scan/bronchoscopy and BAL, and therapeutic drug monitoring results if performed)
- Other relevant treatment/prophylaxis (e.g. antiviral prophylaxis) and positive microbiology results (e.g. *Clostridium difficile,* COVID-19, influenza, cytomegalovirus)
- Details of chemotherapy regimen throughout follow up
- Adverse events/serious adverse events (including AF associated events)
- Date and cause of death

*11.8.3 Blood tests and other routine clinical tests within the trial*

*In the intervention arm*, twice weekly blood tests for GM and BG (aligned with routine clinical bloods).

*In the control (SoC) arm,* routine clinical bloods to be completed as per local usual standard of care.

*In both arms*, bronchoalveolar lavage (BAL) at bronchoscopy for GM BAL (where available) and other SoC microbiological/mycological tests according to the pathways and when allowed (intervention arm) and in, the control arm, at the clinician's discretion.

Routine NHS GM and BG blood and BAL samples that are left over after testing are routinely stored within respective laboratories for various periods of time. As the GM and BG samples for this trial will be treated as routine NHS samples, where possible (and where local policy allows), these leftover samples should be stored at site for future research (see Section 12), which could be in addition or instead of taking optional additional blood samples as part of the optional parallel studies detailed in Section 12 and the *Parallel studies to BioDriveAFS* approved protocol. The patient information and consent forms have been worded accordingly to account for this, allowing patients to consent or decline to storage of these routine samples for use in future research. This is not mandatory for sites to take part in the main BioDriveAFS trial.

## 11.9 Participants receiving a stem cell transplant

As part of their routine care, participants may be referred on to have a stem cell transplant within the 12 month trial follow up period. These participants will remain in the study and be followed up under the intention-to-treat principle (unless they request to withdraw as per Section 11.10). Participant-completed follow up data, including the EQ-5D-5L, will continue to be collected following transplant. Minimal hospital data collection will be expected following a participant's transplant (e.g. date of transplant, mortality and remission status). This should also be completed if a participant goes on to have a transplant outside of the recruiting hospital (e.g. to specialist transplant centres).

If a participant returns to the recruiting hospital following a transplant, it is not expected that intervention arm participants continue with their randomised arm (being monitored with twice weekly BG & GM biomarker blood tests, without antifungal prophylaxis).

## 11.10 Managing change of participant status

Patients will be able to change status and/or withdraw completely from the study at any time without implication. If a patient requests this, the local research team will clarify what aspect of the trial the patient is withdrawing from: for example, withdrawal from ongoing data participation/data collection; withdrawal from a particular aspect of the trial, such as blood collection for storage and/or completion of EQ-5D-5L, etc. Patients who request to change status will be invited to complete a withdrawal form, which will otherwise be completed by the local trial team and sent to the YTU. All participants will be provided with local and central research teams' contact details for queries, etc.

It is unusual for this cohort of patients to lose capacity during treatment. If participants did lose capacity after trial enrolment, we would continue to collect anonymised clinical data from hospitals with no involvement from participants. We would withdraw the participant from completion of patient questionnaires.

### 11.11 End of Trial

The end of the trial will be defined as last patient, last visit (LPLV), the date that the last patient reaches the last follow up time point, i.e. 12 months after randomisation.

The timeline for analysis of the NHS samples (i.e. blood and BAL) and other samples defined in the parallel studies protocol (see Section 12 for outline) will map to the main study timeline. Further use and analysis of samples taken for future research as part of the parallel studies (described in Section 12) or left over, stored NHS samples (described in Section 11.8.3) will be subject to additional permissions from REC. All samples will be destroyed after 5 years from when taken if not used.

## 12 PARALLEL STUDIES TO BIODRIVEAFS – SAMPLE COLLECTION FOR FUTURE RESEARCH (*ONLY AT PARTICIPATING RESEARCH SITES)*

**NOTE**: The current version of the approved full protocol *Parallel studies to BioDriveAFS* will be discussed with sites that are participating in any of these studies as part of their setup, and should be used in conjunction with this main trial protocol at those sites as appropriate.

To summarise on the purpose of these parallel studies, research in this area is moving fast and in the future the NHS might have access to new blood tests and monitoring strategies for fungal infections. It is also important for us to research other areas in this group of patients such as why some patients get a fungal infection and others do not and why the blood tests for fungal infections become positive in some patients but not others (i.e. understanding false positives and negative tests). Such research could lead to better tests or treatments for patients.

We therefore want to take this opportunity to collect some additional samples (blood samples and/or skin/oral swabs, breath and faeces samples) from patients in this study who agree to this (control and intervention arms) and at sites who are able, willing, invited and have funding to do this, for further research/storage, and to be potentially available for future research with the ability to link that research to the other data collected as part of this trial. Collection of samples will be aligned with routine blood tests/clinic visits wherever possible. Where sites are invited and agree to be involved in the parallel studies to BioDriveAFS, a specific, tailored PIL will provided to patients who are approached at that site including the details. Patients will be able to participate in the main BioDriveAFS study without consenting to the parallel studies with no impact on their involvement in the main study or on the quality of their routine clinical care. If the patient chooses to withdraw from the parallel studies, they can request that any stored samples be destroyed.

## 13 SAFETY REPORTING

### 13.1 Risks and anticipated benefits

The published research literature, four PPI meetings, a stakeholder survey, and discussions with key stakeholders, suggests a pragmatic RCT of a biomarker/diagnostic approach to optimising AF use and the management of IFI in AML/ALL/HRMDS/tMPN is feasible, ethical, and required. Published research to date suggests that such an approach can safely result in meaningful reductions in AF use and costs, but further evidence is required within the context of NHS resources and practice. The

BioDriveAFS trial seeks to address the evidence gap using the co-primary endpoints of systemic AF therapy exposure and HRQoL and an adequately powered key secondary endpoint of proven/probable IFI, all of which were identified as the endpoints of most importance to patients and clinical stakeholders. If the trial shows positive results, patients may benefit by not having to take an additional medication during chemotherapy with the absence of the associated adverse effects and drug-drug interactions. There may also be a positive societal effect on antifungal drug resistance as the use of antifungals is optimised.

In the BioDriveAFS trial, clinicians will perform regular blood tests (the biomarkers GM and BG) in the intervention arm that many centres already undertake as some part of routine clinical practice and with which they are familiar. All trial participants will be treated by clinicians as part of routine care who are experts in the care of AML/ALL/HRMDS/tMPN patients and the management of IFI. Measures taken by us, such as our emphasis on good practice and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional patient and system benefits (see above). We will adhere to the Research Governance Framework/ UK Policy Framework for Health and Social Care Research and MRC Good Clinical Practice. The participant information sheet for the study will be developed with the involvement of service users and will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We will make it clear that there is no obligation to participate. Written informed consent will be obtained from all participants after they have had sufficient time to read the study materials and ask questions.

In the unlikely event that new information arises during the trial that may affect participants' willingness to take part, this will be reviewed by the TSC for addition to the patient information leaflet. A revised consent form will also be completed if necessary.

## 13.2 Adverse events

### *13.2.1 Adverse Event (AE)*

The BioDriveAFS trial will comprise adult patients with acute leukaemias undergoing chemotherapy. Prolonged hospital inpatient admission and complex clinical events are usual in this group of patients, will be captured within other Case Report Forms, and do not necessarily require AE reporting. For the purposes of the BioDriveAFS Trial, AEs are defined as any untoward medical occurrence (i.e. any unfavourable and unintended sign, symptom or disease) in a trial participant that logically could or is likely to have a causal relationship with the intervention (i.e. intervention pathway biomarker/diagnostic tests and associated treatments thereof). This could include AEs as a result of, for example, interventions (tests or treatments) that occur because of a false positive biomarker result or AEs due to a lack of an intervention because of a false negative biomarker result. Sites should report AEs when there is concern and consider this in relation to section 13.2.2 below. The study team should be contacted when there is doubt and will help to determine relevance when required. Sites will be encouraged to speak to the trial team for clarification and/or to report a complication as an adverse event if there is any uncertainty from site staff about whether it fits the (S)AE criteria.

The following events do not need to be reported routinely as an AE for this trial unless the criteria above are fulfilled (please also see additional lists under SAEs):

- Respiratory infection or failure, including mechanical ventilation and acute lung injury
- Hepatic infection or failure
- Renal infection or failure, including the need for renal replacement therapy
- Haematologica/coagulation failure, including anaemia, leucopenia, thrombocytopaenia, or pancytopaenia
- Neurological infection or failure
- Unscheduled care escalation
- Infection relapse/recurrence requiring further antimicrobials
- Super- or secondary infection defined as a new infection at a different body site
- Suspected antimicrobial adverse reactions/events
- Progression of the underlying haematological disease or non-response to systemic anti-neoplastic chemotherapy.
- Adverse events related to the anti-neoplastic chemotherapy

Although the above do not require expedited reporting as an AE on the study, key complications will be captured in other routine follow up CRFs. For example, details of fungal infections, and key bacterial and viral infections (including neutropenic fever) will be captured on a monthly basis. Attendance at and admission to hospital for any reason relating to the management of a participant's leukaemia will be captured.

### *13.2.2 Serious Adverse Event (SAE)*

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the YTU.

For the purposes of the BioDriveAFS trial, SAEs will only need reporting if the event:

1) Results in persistent or significant disability or incapacity

2) Consists of a congenital anomaly or birth defect

Other events such as life-threatening events and death (see list below) are also expected in this group of patients and will be recorded by local site research teams as part of routine data collection via the CRF and are therefore not subject to expedited SAE or AE reporting. The following events will not require reporting as a SAE / AE for this trial, but will be captured within the CRF and reported subsequently via trial outputs:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Admission to critical care
- Invasive fungal infection
- Neutropenic fever

- Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed above, other than existing comorbidities.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

### 13.3 Reporting procedures for (S)AEs

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study interventions and/or procedures, will be recorded on the BioDriveAFS Adverse Event Form for return to York Trials Unit.

The following information will be recorded: description, date of onset and end date, assessment of relatedness to study intervention and/or procedures, outcome, expectedness and action taken. Follow-up information should be provided as necessary.

Where repeated adverse events of similar type are observed, these will be discussed with the Data Monitoring and Ethics Committee (DMEC) and will be onward reported should concerns be raised in relation to the type of event and/or frequency observed.

All SAEs will be entered onto the SAE reporting form and sent via REDCap or encrypted email to YTU within 24 hours of the investigator becoming aware of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator (CI) or a medical co-applicant or Trial Steering Committee (TSC) member not acting as a site Principal Investigator (PI). Any change of condition or other follow-up information should be sent as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

SAEs that are deemed to be unexpected and related to the trial will be notified to the REC and sponsor within 15 days. All such events will be reported to the TSC and DMEC at their next meetings.

### 13.4 Pregnancy reporting

It is unlikely a participant of the BioDriveAFS trial will become pregnant during the trial due to the nature of the underlying condition and the associated therapy received by patients.

In the unlikely event that a participant does become pregnant during the trial, this will be reported via the specifically designed case report forms as part of the data collection process. Pregnancy does not necessarily trigger any required change of status for the participant. The Principal Investigator and the participant’s care team will discuss with the participant how to manage this in relation to their treatment and their ongoing participation in the trial, based on their clinical judgement.

# 14 STATISTICS AND DATA ANALYSIS

## 14.1 Statistical analysis plan

Analyses will be described in detail in a Statistical Analysis Plan (SAP), which will be finalised prior to the end of data collection and reviewed and approved by the Trial Management Group and independent oversight committees (Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC)). Analyses will be carried out on a locked dataset and performed using two-sided statistical tests at 5% significance under the principles of intention-to-treat. All analyses will be conducted taking into consideration the reporting requirements of the Consolidated Standards of Reporting Trials (CONSORT) [53].

## 14.2 Sample size calculation

Our sample size is calculated at 404 patients. This trial has two co-primary endpoints and is powered such that success must be shown for both outcomes for the intervention to be deemed beneficial (see Table 4). The comparison of AF use between the two groups is based on showing superiority, while the comparison of EQ-5D-5L index values is based on non-inferiority. The sample size is calculated at 404 patients, as follows.

*Sample size for antifungal therapy use:*
Based on published AF use, we estimate that at least 30% of AML/ALL/HRMDS/tMPN patients will receive ≥3 days of therapeutic systemic AF with AF prophylaxis/SoC [18]. Studies of biomarker-led approaches have shown reductions in AF use >50% [29, 30]. To identify a reduction in this outcome as a dichotomous variable from 30% to 15% of patients, with 90% power and two-sided statistical significance of 5%, and allowing for 20% attrition, requires 404 patients.

*Samples size for health-related quality of life:*
Pickard et al. estimated the minimally important difference for the EQ-5D-3L UK-utility scores in cancer patients (all cancers) to be between 0.09 and 0.12 [54]. McClure and colleagues found a difference of 0.063 for the EQ-5D-5L using simulated data for a general population [55]. Accounting for 15% attrition (participants known to be alive but lost to follow-up; participants who die can be given a score of 0 for any assessment time point following their date of death), a sample size of 404 is required to assess the hypothesis that the intervention is non-inferior to control, based on a non-inferiority margin of 0.07, SD 0.20 [56], 90% power and a 95% two-sided confidence interval.

*Sample size for proven/probable fungal infection (key secondary clinical outcome):*
This will also provide adequate power for the key secondary outcome of proven/probable IFI, to show that the intervention does not increase this outcome by more than 5% provided the proportion in the control group is no more than 2% [18], allowing for 20% attrition.

**Table 4:** *Criteria for decisions about trial effectiveness based on co-primary endpoints*

| | Reduced systemic AF use in intervention arm (statistical superiority) | Equivalent or more systemic AF use in intervention arm |
|---|---|---|
| HRQoL non-inferior | **Effective** | **Ineffective** |
| HRQoL not non-inferior for intervention | **Ineffective** | **Ineffective** |

### 14.3 Internal pilot phase analysis

Relevant data from the internal pilot trial (first nine months of recruitment) will be analysed prior to progression to the main trial to help determine whether continuation is warranted (see section 6.3). The internal pilot progression criteria (table 5) will be used to aid this decision. Analyses will be descriptive in nature; no formal statistical comparisons will be made.

**Table 5:** *Internal pilot progression criteria*

| | **Red** | **Amber** | **Green** |
|---|---|---|---|
| **Average number of patients randomised per site per month** | <0.3 | 0.3-0.59 | ≥0.6 |
| **Number of sites opened** | <9 | 9-12 | ≥13 |
| **Adherence with intervention pathway[a]** | <50% | 50-74% | ≥75 |
| **Collection of valid EQ-5D-5L at month 3 assessment** | <70% | 70-89% | ≥90% |

[a] for intervention participants only, defined as having 3 or more blood tests for GM and BG in the 4 weeks from randomisation

### 14.4 Statistical analysis methods – main trial

Participant flow will be presented in a CONSORT diagram [53]. Baseline data will be summarised descriptively by trial arm, both as randomised and as included in the primary analyses. No formal statistical testing will be conducted on baseline data.

For intervention participants, we will summarise the number and frequency of their blood tests for GM/BG from the start of chemotherapy until neutrophil recovery after the final treatment; the number who undergo a HRCT scan following one or two positive tests but without symptoms; the number who undergo a bronchoscopy and GM BAL; and those prescribed systemic AF therapy among those with/without features of proven/probable IFI. For patients with NF ≥96 hours or other symptoms suggestive of IFI, we will summarise the number who undergo a HRCT (± GM BAL) or other directed tests and/or are prescribed systemic AF therapy, stratified by whether or not their GM/BG remain negative. We will assess the same measures in the comparator group to assess for contamination. We would expect the use of GM/BG during periods of clinical stability (i.e. no neutropenia and/or fever and/or IFI symptoms) to be zero or very low in the control group. We will summarise the use, defined

daily doses and full days of therapy of prophylactic and therapeutic systemic AF for all participants over the course of the trial.

The co-primary outcome of AF use, as a binary outcome, will be analysed via a mixed-effects logistic regression model, adjusting for pertinent participant-level covariates as fixed effects and site as a random effect. EQ-5D-5L index values will be compared between the two groups using a covariance pattern linear mixed model incorporating all post-randomisation assessment points adjusting for baseline value, other pertinent baseline covariates, time, and an interaction between treatment group and time as fixed effects. Participant and site will be specified as random effects. The adjusted mean difference in EQ-5D-5L score over the whole 12 months and at each time point will be calculated with its 95% confidence interval; the treatment effect at 12 months will be the primary endpoint, while the other differences will serve as secondary investigations. The intervention will be deemed non-inferior to usual care if the lower level of the 95% CI is >-0.07 (intervention-usual care; higher score better). The intervention will be considered effective if the co-primary outcomes achieve statistical superiority for a reduction in systemic AF use and non-inferiority for HRQoL as defined in section 14.2 and Table 4). We will present a Complier Average Causal Effect sensitivity analysis for the primary outcomes to account for non-compliance with the intervention and contamination, which considers the number and frequency of bloods for GM/BG taken for participants over the relevant follow-up period.

Secondary outcomes will be analysed using appropriate regression techniques; for example, logistic regression for probable/proven IFI, and the presence of AF associated adverse events; Cox Proportional Hazards regression for survival outcomes (time to all cause and IFI mortality); a proportional odds logistic model for the DOOR outcome; and Poisson regression for count data of number of episodes of NF requiring hospital admission or outpatient management.

### 14.5 Cost-effectiveness analysis

A detailed health economics analysis plan (HEAP) will be drawn up in advance of the analysis. We do not anticipate further analyses assessing the impact of the Covid-19 pandemic on the study results will be required. However, work is currently underway in the trial community on this topic, and should guidance relevant to our trial be published, the HEAP will be updated with the approval of the trial Data Monitoring and Ethics Committee (DMEC) and TSC. All updates will be carried out before the end of data collection.

We will conduct a cost-effectiveness analysis of a biomarker-led diagnostic strategy versus prophylactic AF/SoC for the prevention and management of IFI in AML/ALL/HRMDS/tMPN, using existing evidence in addition to that generated in this trial. The analysis will be undertaken from the NHS perspective, and the methods will be consistent with the NICE Guide to the Methods of Technology Appraisal [57] and Decision Modelling for Health Economic Evaluation [58]. Resource use data will be collected from participating sites using bespoke CRFs, which will be completed by health care staff (i.e. costs associated with prophylaxis/empiric AF, AF related adverse events, biomarker implementation and testing, length of stay, readmissions and follow-up visits related to infections, etc.).

These data will be managed centrally at YTU. Unit costs will be sourced from the NHS Reference Costs databases, the Personal Social Services Research Unit and other appropriate national sources. Health outcomes will be expressed in terms of the quality-adjusted life year (QALY), which will capture the impact of treatment on both mortality and morbidity by ‘weighting’ each period of follow up time by

the value corresponding to the quality of life (using the EQ-5D-5L) during that period. We anticipate there may be certain levels of missing data for resource use and HRQoL. The following approach [59] will be used to impute missing data if necessary. Missing baseline covariate data will be imputed using mean imputation. Multiple imputation with chained equations will be used to impute costs/HRQoL based on patient characteristics and previous costs/HRQoL; this will be done separately for each arm [60].

A within trial analysis with total costs and QALYs will be presented for both trial groups. This analysis will be conducted using regression methods and will assess the short-term effect on patients' health and costs to the NHS of the interventions in our trial. The results of the trial will provide an unbiased estimate of the relative treatment effect of a biomarker-led strategy compared with prophylactic AF/SoC. However, it is unlikely to provide all the evidence relevant to the decision on whether a biomarker-led strategy represents a cost-effective option for the NHS. Hence, a decision-analytic model will be developed to extrapolate the effect on lifetime costs and QALYs combining the best available evidence. A state-transition model will be used in this analysis. State-transition models use a series of health states which demark important changes to prognosis, costs, or quality of life. Parameter estimates, including HRQoL associated with long term consequences of infections, will be sourced from primary data sources, previous modelling studies and the best available evidence from the literature. Systematic searches will be conducted to update the most comprehensive evidence in this area. A 3.5% annual discount rate will be applied for costs and outcomes.

The model will allow an estimate of the cost per QALY gained to be produced, which would allow the cost-effectiveness of the strategies evaluated to be viewed within the context of published NICE cost-effectiveness thresholds (£20,000 and £30,000 per QALY gained). The model will generate lifetime predictions of costs, infection rates, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). Decision uncertainty will be estimated as the probability that each intervention is considered the more cost-effective for a given cost-effectiveness threshold using methods such as cost-effectiveness acceptability curves [61]. The structure of the decision analytic model will be developed in discussion with a group of clinical advisors, experienced haematologists and infection doctors, pharmacists, and other healthcare professionals familiar with the UK NHS.

# 15 DATA MANAGEMENT

## 15.1 Data entry and reconciliation

The data collected by sites will be entered onto the secure web-based REDCap interface. Data will be held securely on a cloud-hosted REDCap server. Access to the study interface will be restricted to named authorised individuals granted user rights by a REDCap administrator at YTU.

The staff involved in the trial (both at the sites and YTU) will receive training on data protection. The staff will be monitored to ensure compliance with privacy standards. A detailed Data Protection Impact Assessment (DPIA) for the trial will be developed for approval by the relevant parties.

Data will be checked according to procedures detailed in the trial specific Data Management Plan.

### 15.2 Data storage and archiving

Each site will hold data according to the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. Data will be collated electronically via the secure online data collection software "REDCap" or paper CRFs and questionnaires in some cases (e.g. where a participant requests completion of a questionnaire in paper form). CRFs will be identified by a unique identification number (i.e. the Trial number) only. A Trial Enrolment Log at the sites will list the ID numbers. YTU will maintain a list of trial numbers for all trial patients at each site. Additional specimens for storage for the purpose of future research will also be identified in this manner.

All YTU data recorded electronically will be held in a secure environment with permissions for access as detailed in the delegation log. The Department of Health Sciences, in which YTU is based at the University of York, has a backup procedure approved by auditors for disaster recovery. Full data backups are performed nightly using rotational tapes, to provide five years' worth of recoverable data. The tape backup sessions are encrypted and password protected, with tapes stored in a locked fire-proof safe in a separate secured and alarmed location. All study files will be stored in accordance with Good Clinical Practice guidelines. Study documents (paper and electronic) held at YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. All essential documents, including source documents, will be retained for a minimum period of five years after study completion, in line with Sponsors' policy. The separate archival of electronic data will be performed at the end of the trial, to safeguard the data for the period(s) established by relevant regulatory requirements. All work will be conducted following the University of York's data protection policy which is publicly available (www.york.ac.uk/records-management/dp/policy).

Additional blood samples taken for storage for the purpose of future research (subject to patient consent to this element of the trial), will be held and processed in accordance with the Human Tissue Act 2004 and the Human Tissue (Scotland) Act 2006. Further details can be found in the parallel studies protocol document.

### 15.3 Participant confidentiality and data protection

The researchers and clinical care teams must assure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a Unique Trial Number, and this will be used on CRFs; patients will not be identified by their name in order to maintain confidentiality.

Data will be processed in accordance with the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. All records will be kept in secure locked locations. All consent forms will be securely stored on password protected, authorised access only, servers and/or in a secure locked cabinet. Clinical information will only be looked at by responsible individuals from the study team, the Sponsor, the NHS Trust, or from regulatory authorities; where it is relevant to the patient taking part in this research as he/she would have agreed to at the time of consent.

## 16 QUALITY CONTROL AND ASSURANCE

### 16.1 Trial Management Group

A TMG has been established to oversee the day-to-day management of BioDriveAFS and is chaired by the Chief Investigators. Other members include the trial statisticians, trial manager, trial coordinators, health economist, qualitative researcher, and other co-applicants. The role of the TMG is

to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet approximately monthly via videoconference/teleconference or in person, with quarterly face-to-face meetings where feasible during the trial.

### 16.2 Data Monitoring and Ethics Committee

The study will be regularly reviewed by the independent Data Monitoring and Ethics Committee (DMEC) composed of independent clinicians and health service researchers with appropriate expertise.

The DMEC will meet routinely to provide project oversight to the trial. This will include monitoring safety and efficacy data as well as quality and compliance data and ensuring that the protocol is accurately followed, and the study is GCP compliant. The committee will recommend whether there are any ethical or safety reasons why the trial should not continue. The independent members of the DMEC committee will be allowed to see unblinded data.

The DMEC will meet at least annually or more frequently if the committee requests. The minutes/records of these meetings will be stored at YTU and will be shared with the sponsor on a routine basis.

### 16.3 Trial Steering Committee (TSC)

An independent TSC has been established to provide overall independent oversight for BioDriveAFS on behalf of the Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The TSC will meet routinely during the trial and will monitor the progress of the trial and provide independent advice. Amongst its members will be an independent chair, a public/patient contributor, a pharmacist, a statistician, a health economist, and clinicians who are independent of the study research team and who have expertise in the research area. A Sponsor representative will also be invited to attend the TSC meeting.

## 17 ETHICAL AND REGULATORY CONSIDERATIONS

### 17.1 Ethics and approvals

We will adhere to the UK Framework for Health and Social Care Research [62] and MRC Good Research Practice Guidance [63]. The PIS for the study will be developed with the involvement of service users and our PPI/PAG groups and will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We will make it clear that there is no obligation to participate. Written informed consent will be obtained from all participants after they have had sufficient time to read the study materials and ask questions. An application for ethical approval will be made in set-up, which will include all participant documentation. We do not anticipate major ethical concerns with this study.

We will seek national Health Research Authority (HRA) & Research Ethics Committee (REC) approval via the Integrated Research Ethics Application System (IRAS) system for the study. The local R&D departments of participating hospitals will approve their involvement in the trial. The trial will be subject to DMEC oversight. The trial manager/CI will submit and obtain approval from the above for all substantial amendments to the original approved documents.

### 17.2 GCP/Declaration of Helsinki

The Investigators will ensure that this study is conducted in full conformity with current regulations, the current revision of the Declaration of Helsinki, and with the ICH Guidelines for Good Clinical Practice.

## 18 PATIENT AND PUBLIC INVOLVEMENT (PPI)

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 (I@Y), 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. In preparation for these sessions, the clinical PPI lead, I@Y and a Leukemia Care advocate produced briefing materials and 'questions to consider.' The discussions took in aspects such as, the burden of medication, quality of life (QoL), toxicities, how information was delivered and the effects on mental health. Participants had personal experience of chemotherapy, the rigors of a cancer diagnosis and therapy for IFI.

A high value was placed on leukaemia research and associated supportive care. Participants had a range of views on the merits of prophylactic antifungals with some stating that additional medications were a burden, but there was also appreciation of the risks of IFI. With respect to our proposed intervention of biomarker-based monitoring there was a high degree of acceptance for this approach as patients already endure frequent phlebotomy; more blood was not considered excessive. With respect to our proposed endpoints of antifungal use, health-related quality of life (HRQoL) and IFI, a high value was placed on HRQoL in relation to excessive oral medication. Tools for the assessment of HRQoL were discussed and the likely impact on the patient experience of having to complete a HRQoL form on a regular basis was explored. 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 completion of this on a regular basis was felt to be practicable. A variety of opinions were expressed on the degree of granularity of some of the domains within EQ-5D-5L as many patients have impaired performance status by virtue of the disease and treatment. However, the visual analogue scale within the EQ-5D-5L was felt to be informative with regards to overall level of function. The PPI sessions conducted provided the basis for selection of the co-primary endpoints of assessing whether the use of biomarkers results in more efficient antifungal use in AML without a deterioration in HRQoL. These sessions also helped our discussion with the AML Supportive Care Subgroup of the National Cancer Research Institute during which this approach was seen as reasonable provided it was supported by PPI and the trial has adequate power to detect a difference in the key clinical outcome of IFI. Our coprimary outcomes, and the adequately powered secondary outcome of proven/probable IFI, therefore encompass the key priorities identified by engagement with both our PPI group and clinical stakeholders.

The clinical PPI lead will manage the PAG with support from I@Y. I@Y is the PPI network at the University of York. It draws together all public involvement in research across the university, as well as serving as a 'hub' for recruitment of patients/the public. I@Y facilitates

networking, provides resources, and supports relationships, and will act as the main point of contact for PAG members. Skilled in engagement, I@Y will liaise and work with the trial team to support the PAG and other public stakeholders.

### 18.1 Summary of PPI activities

The PAG will have 8-10 members with broad skills and a collective remit to advise on any aspect of the trial. Members of the PAG will receive a role description outlining responsibilities. Following initial 'induction' and a meeting with the trial team, to get to know one another and discuss key topics such as 'What is the purpose of PPI/the PAG'? and 'What is a trial?', we will conduct a skills/training 'audit' to understand needs and develop/seek required training, or bespoke by the trial team. The focus of meetings will be determined by the stage of the project and arising matters, but will cover the topics below with flexibility for the PAG to identify/discuss other items:

1. Materials to be used for participants
2. Process evaluation data from the pilot phase; plans for recruitment/retention
3. Main results
4. Dissemination/implementation, engagement/training

In line with UK Standards for Public Involvement, we will ensure that PPI contributors are encouraged and supported to develop confidence, knowledge, and skills. This will include briefing sessions prior to trial meetings to ensure PAG members feel prepared. When the research requires a broader view, we will engage with the wider network (above). While we hope PAG members will be in the trial team throughout, we understand the commitment. We plan to 'check in' with members yearly therefore, to ensure they can continue and provide support if required. If they are unable, we will recruit more members (as above). PAG members will be supported with payments for their time/expenses.

Four PAG members will have 'enhanced' roles; 1 on the Trial Steering Committee and 3 on the Trial Management Group. These members will be the key liaison between trial committees and the PAG, ensuring that the viewpoints and safety of patients remains of primacy, and that trial outcomes are of benefit to patients in the future.

## 19 FINANCING AND INSURANCE

### 19.1 Finance

The BioDriveAFS Trial is funded by the Health Technology Assessment Programme (NIHR132674). The financial arrangements for the study will be as contractually agreed between the funder, the University of York and the Sponsor (Hull University Teaching Hospitals NHS Trust).

### 19.2 Insurance

This is an NHS-sponsored research study, sponsored by Hull University Teaching Hospitals NHS Trust. If there is negligent harm during the trial, when the NHS Trust owes a duty of care to the person harmed, NHS Indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the Trust R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

# 20 DISSEMINATION AND PROJECTED OUTPUTS

Results from this study will be written up and submitted to peer-reviewed journals. A publications policy will be generated in advance to detail authorship, acknowledgements and review processes for any publications arising from the BioDriveAFS Trial.

All publications, presentations, correspondence and advertisements arising or related to the grant must acknowledge the funder using the National Institute for Health and Care Research (NIHR) approved disclaimer.

## 20.1 Core outputs

Other core outputs from this trial will include:

- Quantitative and qualitative process evaluation data to inform the pathway to adoption and dissemination/implementation, and other AFS interventions and the wider AFS agenda
- A training, engagement and PPI legacy built around the development of a network of stakeholders interested in this aspect of AFS and the wider AFS agenda
- The results of this trial are likely to be practice changing/informing and are therefore highly likely to be incorporated into national and international guidelines
- Publications in high-impact open-access journals relating to the work packages as outlined
- Conference presentations at high-impact, relevant national and international conferences relating to the key components of the work packages: trial design, main trial, process evaluation and cost-effectiveness
- Cost-effectiveness data to inform the NHS about the value for money of our intervention
- A potential research resource for the global research community to perform further research relating to the stored blood samples with linked clinical data, as outlined above
- Development and use of a desirability of outcome ranking (DOOR) endpoint as an exploratory outcome to assess relevance within the context of this trial and AFS

## 20.2 Dissemination strategy

Dissemination will be integrated with the process evaluation (NHS staff) and PPI (public) work, which will produce outputs, including the identification of barriers and facilitators, that will inform adoption and implementation in the NHS, including, for example, the optimal approaches to messaging, marketing, and communication.

Engagement will continue to take place with key stakeholders, partners and collaborators as part of the dissemination strategy. These include relevant charities and patient organisations, relevant NIHR Applied Research Collaboratives, key opinion leaders (e.g. in AFS, infection and haematology), the AML-SCS, and other relevant stakeholder organisations such as laboratories performing IFI related tests, Royal Colleges, and specialist societies such as the British Infection Association, the British Society for Haematology, the British Society for Medical Mycology and the Royal Pharmaceutical Society.

### *20.2.1 Targeted clinical dissemination in collaboration with the British Society for Antimicrobial Chemotherapy (BSAC)*

A partnership has been agreed with the British Society for Antimicrobial Chemotherapy (BSAC) to help deliver key engagement and post-trial adoption, training, and implementation for example through the following:

- A BSAC hosted, bespoke networking/project website (E-forum) to facilitate and enhance sharing and communication of research outputs. Resources from webinars and training events will be housed on this site, which will provide key output legacy and reusable and updateable materials that are available beyond the timeframe of the project
- Hosting of a national trial related event and series of up to four separate webinars to promote dissemination of research outputs, stakeholder involvement and networking. Recordings of events will be hosted on the BSAC e-learning hub (https://www.infectionlearninghub.co.uk/)
- Development of an accredited e-learning course relating to project outputs. The course will be hosted on the FutureLearn Platform https://www.futurelearn.com/ and developed as a SCORM (Sharable Content Object Reference Model) compliant course to enable NHS trusts to download and deploy on local intranets
- Outputs of webinars and other meetings as potential leading articles in BSAC journals
- Appropriate use of social media to engage with the public, professionals, and stakeholders

## 20.3 Access to data

A statement of permission to access source data by study staff and for regulatory and audit purposes will be included within the patient consent form with explicit explanation as part of the consent process and Participant Information Leaflet.

In principle, once YTU has completed the analysis and completed all intended outputs, anonymised data will be made available for meta-analysis and where requested by other authorised researchers and journals for publication purposes. Requests for access to data will be reviewed by the Chief Investigator and study Sponsor.

The Investigator(s)/Institutions will permit monitoring, audits, and REC review (as applicable) and provide direct access to source data and documents.

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