Early versus Late Stopping of Antibiotics in Children with Cancer and High-risk Febrile Neutropenia (ELSA FN)

Statistical Analysis Plan

Version 1
02 March 2026
Clinicaltrials.gov ID NCT04948463

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List of Abbreviations

AE	Adverse Event
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
CDI	Clinically Defined Infection
CI	Confidence Interval
CPG	Clinical Practice Guideline
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data Safety Monitoring Committee
EMR	Electronic Medical Record
FN	Febrile Neutropenia
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
HCT	Haematopoetic Stem Cell Transplant
ICU	Intensive care unit
ITT	Intent-To-Treat
LOS	Length of Stay
LOT	Length of Therapy
MDI	Microbiologically Defined Infection
MET	Medical Emergency Team
MRSA	Methicillin Resistant Staphylococcus Aureus
OPA	Our Practice Advisory alert (formerly known as Best Practice Advisory)
RCH	Royal Children's Hospital
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SQL	Structured Query Language
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMP-SMX	Trimethoprim / sulfamethoxazole

1. ADMINISTRATIVE INFORMATION

Protocol: ELSA-FN; V6.3 13 March 2025
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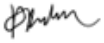
Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
02 March 2026	1.0	Alannah Rudkin		Initial release.	Not applicable.

Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

Name	Role on Study	Affiliation	Signature	Date
Alannah Rudkin	Biostatistician and project officer	Murdoch Children's Research Institute		02 March 2026
Anneke Grobler	Biostatistician	Murdoch Children's Research Institute		2 March 2026
Gabrielle Haeusler	Principal Investigator	Murdoch Children's Research Institute. Royal Children's Hospital. Peter MacCallum Cancer Centre		17 March 2026
Coen Butters	Investigator	Murdoch Children's Research institute. John Hunter Children's Hospital		17 March 2026

2. STUDY SYNOPSIS

This randomised controlled non-inferiority trial will compare stopping empiric antibiotics prior to absolute neutrophil count (ANC) recovery (STOP) to standard of care (SOC) in children with cancer and high-risk febrile neutropenia (FN). This is a single site trial embedded into the electronic medical record (EMR) at the Royal Children's Hospital Children's Cancer Centre in Melbourne. This study planned to recruit 312 children (156 per arm) with high-risk FN in 48 months. Participants will be randomly assigned to short-course antibiotics or standard of care and followed up for 28 days.

This study design was chosen in discussion with key stakeholders from oncology, infectious diseases and consumer representatives. It is based on the assumption that the primary outcome "unfavourable clinical course" occurs with similar frequency in both arms.

2.1 Study definitions

As this study is fully embedded into the EMR all 'clinical trial definitions' were translated to 'EMR definitions.' These are defined as follows:

Clinical definitions describe conditions based on clinician assessment, symptoms, signs, and diagnostic reasoning, reflecting real-world clinical decision-making. They prioritise clinical judgement but may vary between clinicians and sites and are not always directly or consistently captured in structured electronic data.

EMR-based definitions (also termed operational or digital phenotypes) translate clinical concepts into reproducible combinations of structured electronic health record elements such as orders, medications, observations, and coded diagnoses. They prioritise standardisation, scalability, and automated ascertainment, enabling consistent outcome measurement and trial conduct within the EMR, but may incompletely capture clinical nuance.

Neutropenia
Absolute neutrophil count (ANC) < 0.5 x 10^9/L or total white cell count (WCC) <1 x 10^9/L

Febrile neutropenia onset
Clinical definition: First onset of fever in the setting of neutropenia.
EMR definition: Fever within 24h of recorded neutropenia (pre- or post-fever) or recorded triage time if presenting to the emergency department with FN as reason for admission.

New FN episode
Clinical definition: A new fever occurring during a new episode of neutropenia and more than 28 days after last randomisation.
EMR definition: Neutropenia and a new fever occurring after the 'end of FN episode' and more than 28 days after last randomisation.

Neutrophil/ absolute neutrophil recovery
ANC >= 0.5 x 10^9/L

FN antibiotics
Any of piperacillin-tazobactam, cefepime, ceftazidime, ciprofloxacin, +/-vancomycin

Please refer to protocol appendix 4: EMR definitions for more detail.

2.2 Early termination of trial

The trial ended before it could reach its planned sample size. The initial trial protocol planned to recruit from November 2021 until November 2024. The trial had sufficient funding and resources to extend recruitment and closed to recruitment at the end of November 2025.

Expected recruitment was extrapolated from febrile neutropenia data collected as part of a national observational study (PICNICC). However, recruitment was well below expected rates for several reasons including (i) COVID-19 pandemic and change to pattern of febrile episodes in this population and (ii) introduction of new ALL treatment protocol that mandated antibiotic prophylaxis not previously used. Together, these impacted the frequency of febrile presentations, including infective and non-infective causes. Finally, the number of febrile neutropenic patients recorded as 'clinically unsuitable' was also higher than anticipated including patients who had prolonged fever or a confirmed bacterial infection.

As the trial progressed clinicians became more comfortable with stopping antibiotics and discharging patients early, which may have also reduced the number of febrile neutropenic episodes available for randomisation.

It would have taken over a decade to recruit the full sample size, by which time the clinical relevance of the results would be comprised. The trial did not have sufficient funding or resources to extend to other sites to bolster the recruitment numbers.

2.3 Primary Objective

To determine if stopping antibiotics prior to ANC recovery in children with cancer and high-risk FN is non-inferior to standard of care.

2.4 Secondary Objectives

To determine the impact that stopping antibiotics prior to ANC recovery, as compared to standard of care, has on:

1. Recurrence of temperature ≥38 degrees Celsius (ie. new fever episode after afebrile period of 48h)
2. Clinical instability (one or more of conscious state, respiratory rate, blood pressure, heart rate, oxygen saturation meeting mandatory emergency call criteria OR two or more respiratory rate, blood pressure, heart rate or oxygen saturations simultaneously (+/- 4h) meeting clinical review criteria)
3. Admission to intensive care unit
4. Admission to intensive care unit for organ support
5. New positive blood culture
6. 28 day all-cause and infection-related mortality
7. Duration of neutropenia (measured as days from ANC <500 cells/mm3 or absence of neutrophils to ANC ≥500 ells/mm3)
8. Total antibiotic duration (days of therapy)
9. Total hospital length of stay (LOS)
10. Readmission to hospital (inpatient ward) within 28 days of randomisation
11. Development of C. difficile infection
12. Development of an antibiotic-resistant infection or colonisation within 28 days of randomisation

ELSA-Impact
13. Clinician confidence and acceptability
14. Patient/parent/caregiver confidence and acceptability

2.5 Study Population

The eligible trial population will include children admitted to the Royal Children's Hospital (RCH) with high-risk FN, defined as FN occurring in patients with an underlying diagnosis of Acute Myeloid Leukaemia (AML); Acute Lymphoblastic Leukaemia (ALL) in dose-intensive treatment phases (induction, consolidation, intensification); lymphoma in induction; ALL or acute lymphoblastic lymphoma (LLy) on Total Therapy Study 17 (TOT17) protocol, or patients with any diagnosis who are within 100 days post allogeneic HCT.

2.6 Intervention

Short course antibiotics (STOP): Intravenous empiric FN antibiotics (any of: piperacillin-tazobactam, cefepime, ceftazidime, ciprofloxacin, +/-vancomycin) will be administered according to current RCH FN clinical practice guideline (CPG) and dosing protocols. Antibiotics will be commenced at onset of FN (as per RCH CPG) and stopped once afebrile and clinically stable for 48 hours.

Standard of care (SOC): Intravenous empiric FN antibiotics (any of: piperacillin-tazobactam, cefepime, ceftazidime, ciprofloxacin, +/-vancomycin) will be administered via current RCH FN CPG and dosing protocols. Antibiotics will be commenced at onset of FN (as per RCH CPG) and continued until resolution of fever, clinical recovery and ANC as determined by the treating clinicians but usually ≥ 500 cells/mm^3.

2.7 Randomisation and Blinding

Study participant febrile neutropenic episodes will be randomly assigned, in a 1:1 ratio to the 2 study groups. A statistician other than the trial statistician prepared the randomisation schedule using block randomisation to maintain balance between treatment arms. The randomisation schedule was uploaded to the REDCap system at commencement of the study. Participants can be randomised to the trial multiple times for separate episodes of febrile neutropenia. Trial participants and care providers will not be blinded to trial group assignment. Blinding of trial participants and care providers is not appropriate in this study. However, the study team are blinded to future randomisation (allocation concealment).

Patients are considered randomised if they have been assigned a study ID in REDCap. Any erroneous randomisations will not be exported from the REDCap randomisation list for merging. This is the circumstance in which a randomisation slot was accidentally accessed and used but not assigned to a participant e.g. an EMR analyst assumed this was a training environment. There We expect only two erroneous randomisations in REDCap.

Consent definitions
Consent EMR alert with a consent – response of 'Patient consented'
Eligible patient episodes are episodes were an EMR consent alert appeared and was not marked as 'Not clinically suitable'. This includes 'Patient consented', 'Patient Declined', or if alert was dismissed.

2.8 Sample Size

<u>Target sample size</u>

When the sample size in each group is 147, a two-group large-sample normal approximation test of proportions with a one-sided 2.5% significance level will have 80% power to reject the null hypothesis that the test and the standard care not equivalent (the difference in proportions is 0.15 or farther from zero in the same direction) in favour of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0 and the proportion in the standard group is 0.3.

This sample size assumes that all participants are independent, however, some participants can be enrolled in the trial more than once. This can be accommodated in the sample size calculation by a design effect. We calculated the design effect to be 1.06. This is calculated using the formula in Yelland et al (1) assuming that 50% of enrolments will be enrolled only once, and the rest would be enrolled more than once, that the proportion in the intervention group was 0.3 and 0.3 to 0.33 in the control group. ρ is assumed to be 0.3. When we apply the design effect to the sample size calculated the final sample size is 156 per arm or 312 in total.

Actual sample size
The ELSA-FN trial was able to randomise 55 neutropenic episodes (28/27 split between arms).

2.9 Study Procedures

As an embedded trial, assessments occur continuously while the patient is admitted to hospital. This includes routine monitoring of vital signs, clinical review as indicated and further blood cultures/intervention as clinically indicated. This information is captured by the EMR and will be used as part of the dataset.

Eligible patients will be identified by an EMR alert. Patients will be initially screened for eligibility based on underlying cancer diagnosis. All patients with eligible diagnosis that are (i) admitted for neutropenic observation (i.e. admitted with neutropenia and placed on 'high-risk' FN care pathway awaiting fever); (ii) admitted to inpatient ward with FN or (iii) develop FN while an inpatient but not on high-risk FN care pathway will be approached by the study team to discuss participation in the trial. Patients will be considered screened for the study if the EMR triggers a consent Our Practice Advisory (OPA) based on the programmed eligibility criteria. Following documentation of consent, patients will be enrolled and randomised electronically, provided all inclusion and exclusion criteria are fulfilled at the time of randomisation. While every effort will be made to consent patients before or within the first 48 hours of FN onset, patients may be consented, enrolled and randomised up to 96 hours after resolution of fever, provided they continue to meet all inclusion criteria and none of the exclusion criteria.

Eligibility screening, enrolment, randomisation and collection of FN demographic, onset/episode and outcome data will be collected automatically by the EMR system up until 28 days after randomisation.

2.10 Deviations from Protocol

No sensitivity analysis or supplementary analysis described due to the small sample size. Fever without focus was removed from the new infection secondary outcome even though it was listed in the protocol.

Full details of the background to the trial and its design are presented in the protocol

3. GENERAL STATISTICAL METHODOLOGY

3.1. Objectives of Analysis Plan

This analysis plan describes the presentation of baseline demographic data and analysis of all primary and most secondary outcome. It excludes the analysis of the qualitative data collected from the focus groups with clinicians and parents and excludes the cost-effectiveness analysis (ELSA Impact).

3.2. Analysis Software

All analyses will be conducted using Stata statistical package of at least version 19.

3.3. Data verification

This data is extracted from the EMR and saved in csv format. These data tables are then cleaned and labelled in Stata or R using a do file.R script saving in a .dta or .csv format ready for analysis. This data preparation will be performed by the project officer and data analyst within the Centre of Health Analytics.

Any data queries discovered during the analysis can be raised with the study team who can investigate further. Any changes made to the data after a data query must be documented in a Stata do file and the updated data shared with the study biostatistician.

The clinical team will verify the data for clinician correctness, they will be given the cleaned data in the desired format (excel).

3.4. Definition of Baseline

Baseline is considered as up to randomisation and includes febrile neutropenia onset.

3.5. Definition of analysis populations

All variables will be analysed using an intent-to-treat analysis unless otherwise specified.

3.6. Definitions related to Adverse Events (AEs)

For the purposes of this trial the investigator is responsible for recording any related AEs in the intervention arm, with the following exceptions:

- Conditions that are present at screening and do not deteriorate will not be considered adverse events.
- Abnormalities in blood parameters including renal function (creatinine), liver function tests (LFTs) and Full Blood examination (FBE). These parameters are impacted by underlying chemotherapy and not early stopping of antibiotics.

Serious Adverse Event (SAE): Any adverse event/adverse reaction that results in:

- Bacteremia episodes from randomisation to neutrophil recovery (ANC>500 cells/mm3)
- ICU admission within 28 days of randomisation
- Death within 28 days of randomisation

AEs will be reported with their description, seriousness, relatedness, and grade. This study uses the Common Terminology Criteria for Adverse Events (CTCAE) reporting version 5 to grade adverse events.

3.7. Adjustment for Multiplicity

Multiplicity in this trial has been controlled by using a composite primary outcome. This avoids the inflated type I error associated with having five individual primary outcomes.

3.8. Handling of Missing Data

The primary outcome, 'unfavourable clinical course' will be reviewed by the study investigator for accuracy and completeness before the database is finalised and sent to the biostatistician.

As this trial is embedded in the EMR, measurement of outcomes is defined by their presence or absence in the EMR. For example, if a patient doesn't have a temperature over 38 degrees recorded in the EMR, they are documented to not have had recurrence of fever.

Patient/parent and clinician acceptability relies on the investigator overriding the STOP arm allocation entering a reason for continuing antibiotics. If the antibiotics aren't stopped but no reason is entered, this data will be considered missing.

Any missing primary outcome data for unfavourable clinical course will be considered missing at random. The main factors that could influence missing data for a recurrence of temperature, clinical instability, or a new positive blood culture would be that a patient is well enough to be discharged from hospital (admission status known) so the results weren't recorded. Admission to RCH intensive care unit (ICU) and inpatient death are highly unlikely to be missing for any reason.

As the primary outcome for this study is a composite outcome, if any of the non-missing components are present (e.g. admission to ICU documented) then unfavourable clinical course can be considered present.

3.9. Definitions Related to Estimands

Section 5 and 6 report analytical approaches for the primary and secondary outcomes using the estimand framework. An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It has 5 attributes: population, treatment, variable of interest e.g. outcome, summary measure, and possible intercurrent events (defined as an event that can occur post-randomization and preclude or affect the interpretation of the variable of interest e.g. discontinuation of treatment).

When defining an estimand, it must be made clear how intercurrent events will be handled in the analysis. Different approaches can be taken towards handling intercurrent events and are described below:

i) Hypothetical: a strategy which envisages a scenario in which the intercurrent event would not occur, e.g. if participants had not continued antibiotics or if death had not occurred
ii) Treatment policy: a strategy which seeks to understand the treatment effect on the variable regardless of the intercurrent event, i.e. an outcome is of interest whether or

not the intercurrent event occurred prior to the outcome, e.g. the final outcome is of interest irrespective of whether the participant stops antibiotics

iii) Composite: a strategy which considers the occurrence of the intercurrent event as informative about the participants outcome. Under this strategy the intercurrent event is included in the endpoint definition, e.g. classifying the use of rescue medication as failure, in addition to disease progression, in a time-to-event analysis

iv) Principal Stratification: a strategy wherein treatment effects are assessed in the stratum of participants who would have a specific status with respect to the intercurrent event e.g. examining the effect of treatment in participants who would not require rescue medication

v) While-on-treatment: a strategy which considers response to treatment prior to the occurrence of the intercurrent event to be of interest. For repeated measures, values up to the intercurrent event are of interest but not values after the intercurrent event. Generally this strategy is only useful if the duration of treatment is not relevant either because it is not clinically relevant or because the rate of an event or outcome is constant over time e.g. the rate of adverse events, where one assumes a constant hazard.

4. DESCRIPTIVE STATISTICS

4.1. Recruitment and Follow-up

Recruitment numbers (number consented and randomised), including reasons for not consenting or randomising, will be summarised. Numbers will be presented in a CONSORT flowchart. This information can be supplied by the study team if not available in the exported data. A listing will be provided of any free-text reasons for override of EMR alerts or comments listed by clinicians during consent and randomisation.

4.2. Baseline Characteristics

All baseline demographic information will be presented by treatment arm. For continuous variables mean (standard deviation SD) or median (interquartile range IQR) will presented. For categorical variables proportions will be listed. Unless otherwise specified all demographic data is at time of randomisation per neutropenic episode.

Participants demographics
Number of participants randomised into each arm, and overall.
Number of febrile neutropenia episodes in each arm and overall.
Age at randomisation (years), sex, disease type (type of leukaemia, lymphoma or HCT), treatment phase if ALL (e.g. induction), days post-HCT at randomisation, central venous access (i.e. none, peripherally inserted central catheter, Hickman or portacath), prescribed antimicrobial antibiotic prophylaxis (i.e. ciprofloxacin, levofloxacin), PJP Prophylaxis (TMP-SMX, dapsone, pentamidine) and antifungal prophylaxis, (amphotericin B, liposomal amphotericin, fluconazole, posaconazole, voriconazole, itraconazole, micafungin, caspofungin) in previous 7 days, and prescribed granulocyte colony stimulating factor (G-CSF) in previous 7 days.

Febrile neutropenia episode onset demographics
Location at FN onset (outpatient or ward), date and time of FN onset (inpatient onset) or triage (outpatient onset), maximum documented temperature (within 4 hours of onset of FN), ANC at FN onset, fluid bolus (≥ 10 ml/kg volume) within 4 hours of FN onset, blood pressure below and/or heart rate above 95th percentile for age at time within 4 hours of FN onset, and mucositis present at randomisation.

4.3. Compliance

For each arm we will summarise the participant episodes who were compliant. Compliance for each arm is defined as follows:

Compliance in STOP arm
Participant episodes who were randomised to the STOP arm will be considered compliant if antibiotics are ceased after randomisation during same period of neutropenia.

Ceased after randomisation – no further febrile neutropenia antibiotic* doses given after randomisation

Compliance in standard of care arm.
Participant episodes randomised to the SOC will be considered compliant if febrile neutropenia antibiotics were continued after randomisation until evidence of neutrophil recovery (0.2-0.5 x 10^9/L)).

* New administration of antibiotics given for infection or new fever would not be counted as non-compliance in STOP arm if antibiotics were stopped.

Graphical representation of antibiotic duration and neutropenia
As presented in the statistical analysis plan (4) for the Vissing and Schmiegelow trial (2) in Denmark, a descriptive plot showing the days of antibiotics coloured coded by randomised arm and days of neutropenia will be generated. Day 0 will be randomisation with negative days showing when antibiotics started.

A histogram will also be created summarising duration of antibiotics in each treatment arm.

4.3. Concomitant Therapies

Prescribed antibiotic prophylaxis (i.e. levofloxacin, ciprofloxacin, TMP-SMX, other), antifungal prophylaxis (i.e. fluconazole, voriconazole, other) and granulocyte colony stimulating factor (G-CSF) will be summarised by treatment arm.

5. PRIMARY OUTCOME(S)

5.1. Analysis

Population Children with high-risk FN

Treatment
Randomised to short course antibiotics (STOP) versus standard of care (SOC) antibiotic treatment for high-risk febrile neutropenia regardless of treatment received

Outcome
The primary outcome is 'unfavourable clinical course' defined as any of, and occurring during the same episode of severe neutropenia:

- Recurrence of temperature ≥38 degrees Celsius (i.e. new fever episode after afebrile period of at least 48 hours)
- Clinical instability (one or more of conscious state, respiratory rate, blood pressure, heart rate, oxygen saturation meeting mandatory emergency call criteria OR two or more respiratory rate, blood pressure, heart rate or oxygen saturations simultaneously (+/- 4h) meeting clinical review criteria)
- Admission to the ICU
- New positive blood culture collected after randomisation (with any organism)
- Death

Summary measure
Risk difference (difference in proportions) with 95% confidence interval (CI).

Intercurrent Events

1. Participant febrile neutropenic treatment was non-compliant with randomisation

Strategy for Intercurrent Event
Treatment policy strategy will be used to handle all intercurrent events.

Analysis
The difference in proportion of unfavourable clinical course episodes between the two randomised treatment arms (with a 95% CI) will be estimated using a generalised linear mixed model (GLMM) with a logit link function and Bernoulli distribution with random effects for participant. A fixed effect will be added for HCT episode (binary outcome, HCT episode or non-HCT episode). The number and percentage (with 2-sided 95% CI) of unfavourable clinical course episodes will also be estimated for each arm. The upper limit of the CI will be compared to the pre-specified non-inferiority margin (15%).

No sensitivity or supplementary analyses are planned.

Stata code

```
melogit outcome i.arm i.HCT || participant_id :
margins i.arm, post
lincom _b[1.arm] - _b[0.arm]
```

5.2. Subgroup Analyses for primary outcome

The number and percentage of unfavourable clinical course episodes will be summarised for diagnosis type (ALL, AML, lymphoma, HCT) by arm.

Stata code where diagnosis is coded 1-4 for type

```
forvalues x=1/4{
dtable i.outcome if diagnosis==`x', by(arm)
}
```

6. SECONDARY OUTCOMES

Population
Children with high-risk FN

Treatment
Randomised to short course antibiotics (STOP) versus standard of care antibiotic treatment for high-risk febrile neutropenia regardless of treatment received

Intercurrent Events
1. Participant febrile neutropenic treatment was non-compliant with randomisation

Strategy for Intercurrent Event
Treatment policy strategy will be used to handle all intercurrent events.

6.1 Secondary outcome – fever

6.1.1. Recurrence of fever

Outcome
Fever (temperature ≥38 degrees Celsius)
1. Recurrence of fever during the same period of neutropenia. The same period of neutropenia is defined as the period from randomisation until neutrophils reach 0.5 x 10^9/L after randomisation.
2. Recurrence of fever within 28 days of randomisation (regardless of neutropenia)

Summary measure
Risk difference (difference in proportions) with 95% confidence interval (CI).

Analysis
The number and percentage (with 95%CI) of febrile neutropenic episodes with at least one fever recurrence during the same period of neutropenia (outcome 1) and within 28 days of randomisation (outcome 2) will be summarised for each arm and analysed as per Section 5.1.

6.1.2. Duration (hours) of temperature

Outcome
1. Duration (hours) of temperature ≥38 degrees Celsius during the same period of neutropenia (until neutrophils reach 0.5 x 10^9/L after randomisation)
2. Duration (hours) of temperature ≥38 degrees Celsius within 28 days of randomisation (regardless of neutropenia)

Duration will be calculated by the number of days within the relevant period (neutropenia or 28 days) with a temperature recorded in the EMR ≥38 degrees Celsius.

Summary measures
Mean difference in duration of temperature

Analysis
The mean duration of temperature (with 95%CI) in each treatment arm will be summarised during the same period neutropenia (outcome 1) and within 28 days of randomisation (outcome 2). The difference in mean (with 95% CI) duration of fever between the arms will be estimated using a

linear mixed effects regression model using an identity link function and a normal distribution with repeated measures with random effects for participant and fixed effect for HCT episode. The upper limit of the two-sided CI will be compared to the pre-specified non-inferiority margin of 4 hours.

The mean (with 95% CI) duration of fever will be summarised for diagnosis type (ALL, AML, lymphoma, HCT) by arm.

Stata code

```
meglm outcome i.arm i.HCT || participant_id :
margins i.arm, post
lincom _b[1.arm] - _b[0.arm]
```

Stata code where diagnosis is coded 1-4 for type

```
forvalues x=1/4{
dtable outcome if diagnosis==`x', by(arm)
}
```

6.2 Secondary outcome – clinical instability

Outcome
Clinical instability (one or more of conscious state, respiratory rate, blood pressure, heart rate, oxygen saturation meeting mandatory emergency call criteria OR two or more respiratory rate, blood pressure, heart rate or oxygen saturations simultaneously (+/- 4h) meeting clinical review criteria) within same period of neutropenia (outcome 1) or within 28 days (outcome 2).

See appendix A for more detail on clinical instability definitions.

Summary measure
Risk difference (difference in proportions) with 95% confidence interval (CI).

Analysis
The number and percentage (with 95% CI) of febrile neutropenic episodes with at least one instance of clinical instability during the same period neutropenia (outcome 1) and within 28 days of randomisation (outcome 2) will be summarised for each arm and analysed as per Section 5.1.

6.3 Secondary outcome – Admission to ICU

Outcome
Admission to ICU during the same period of neutropenia (outcome 1) or within 28 days (outcome 2).

Summary measure
The number and percentage (with 95%CI) of admissions to ICU during the same period of neutropenia (outcome 1) and within 28 days of randomisation (outcome 2) will be summarised for each arm and analysed as per section 5.1.

6.4 Secondary outcome – Admission to ICU for organ support

Outcome
Admission to ICU for organ support during the same period of neutropenia (outcome 1) or within 28 days (outcome 2).

Defined as admission to ICU in which management includes any of the following:
- Inotropes/vasopressors: adrenaline, noradrenaline, dopamine, dobutamine, vasopressin, milrinone
- Renal replacement therapy: continuous renal replacement therapy, intermittent haemodialysis, peritoneal dialysis
- Invasive ventilation: mechanical ventilation
- Non-invasive ventilation: bi-level positive airway pressure (BiPAP), continuous positive airway pressure

Summary measure
Risk difference (difference in proportions) with 95% CI.

Analysis
The number and percentage (with 95% CI) of febrile neutropenic episodes with any admission to ICU with organ support during the same period neutropenia (outcome 1) and within 28 days of randomisation (outcome 2) will be summarised for each arm and analysed as per section 5.1.

6.5 Secondary outcome – New positive blood culture

Outcome
New positive blood culture during the same period of neutropenia. This is a blood culture collected after randomisation and during the same period of neutropenia that becomes culture-positive with any organism.

Summary measure
Risk difference (difference in proportions) with 95% CI.

Analysis
The number and percentage (with 95% CI) of febrile neutropenic episodes with at least one positive blood culture during the same period neutropenia will be summarised for each arm. Analysis as per section 5.1.

6.6 Secondary outcome – New infection

Outcome
New infection during the same period of neutropenia (outcome 1) or within 28 days (outcome 2).

Defined as:
1. Microbiologically defined infection (MDI) – an infection that is clinically detectable and microbiologically proven, ncludes bloodstream (bacteraemia) and non-bloodstream (stool, sputum, urine etc)
2. Clinically defined infection (CDI) – an infection that is clinically diagnosed, but no pathogen is identified

New infections as manually reviewed by the trial investigators and recorded in the adverse event activity (and review spreadsheet).

Summary measure
Risk difference (difference in proportions) with 95% CI.

Analysis
The number and percentage (with 95% CI) of febrile neutropenic episodes with at least one 1.) MDI or 2.) CDI infection during the same period of neutropenia (outcome 1) and within 28 days of randomisation (outcome 2) will be summarised for each arm. These will entail 4 separate analyses, one for each outcome.

6.7 Secondary outcome – Mortality

Outcome
1. All cause 28-day mortality
2. Infection-related 28-day mortality (death with microbiologically proven or clinically suspected infection)

Summary measure
Risk difference (difference in proportions) with 95% CI.

Analysis
The number and percentage (with 95% CI) of febrile neutropenic episodes with a recorded death (due to any cause) within 28-days of randomisation summarised by arm.
This will also be summarised by infection-related deaths.
Analysis as per section 5.1.

6.8 Secondary outcome – Duration of neutropenia

Outcome
Duration of neutropenia (days) from fever onset to first ANC ≥0.5 x 109/L. Censored at 28 days after randomisation if no neutrophil recovery.

Summary measure
Difference in means with 95% CI.

Analysis
Mean (with 95%CI) duration of neutropenia in each arm estimated using a linear mixed effects regression model with repeated measures with random effects for participant
using a generalised linear mixed model (GLMM) with an identity link function with random effects for participant and fixed effect will be added for HCT episode (binary outcome, HCT episode or non-HCT episode). Analysis as per section 6.1.2. The upper limit of the two-sided CI will be compared to the pre-specified non-inferiority margin of 1 day.

6.9 Secondary outcome – Antibiotic duration

6.9.1 Antibiotic duration

Outcome

1. Total antibiotic duration measured as length of therapy (LOT) from randomisation and within 28 days from randomisation (excluding antibiotic prophylaxis). Total calendar days on any antimicrobial (multiple drugs on one day count as 1 day).
2. Total antibiotic duration measured as days of therapy (DOT) from randomisation and within 28 days from randomisation (excluding antibiotic prophylaxis). Days per antimicrobial agent (each drug adds another DOT per day).

Summary measure
Difference in means with 95% CI.

Analysis
The mean duration of antibiotics (with 95%CI) in each treatment arm will be summarised. The difference in mean (with 95%CI) duration between the arms as per section 6.1.2. The upper limit of the two-sided CI will be compared to the pre-specified non-inferiority margin of 1 day.

6.9.2 Antibiotic reinstalment

Outcome
A binary indicator of re-instalment of antibiotic after initial FN antibiotic stopped within 28 days. The antibiotic order and administration must be after randomisation.

Summary measure
Risk difference with 95% CI.

Analysis
The number and percentage (with 95%CI) of reinstalments of antibiotics for episodes within 28-days of randomisation summarised by arm.

Analysis as per section 5.1.

6.10 Secondary outcome – Hospital length of stay

Outcome
Total hospital length of stay (LOS). Censored at 28 days after randomisation if not discharged.

1. Length in days of primary admission (from randomisation to first hospital discharge)
2. Total number of admitted days between randomisation and day 28

Summary measure
Mean difference (with 95% CI) between arms

Analysis
The mean total hospital LOS (with 95% CI) in each treatment arm will be summarised. The difference in mean (with 95% CI) total hospital LOS between the arms as per section 6.1.2. The upper limit of the two-sided CI will be compared to the pre-specified non-inferiority margin of 1 day.

6.11 Secondary outcome – Unplanned readmission to hospital

Outcome
Any unplanned readmission to hospital (inpatient ward) within 28 days of randomisation.

Summary measure
Risk difference (difference in proportions) with 95% CI.

Analysis
The number and percentage (with 95%CI) of having at least one unplanned admission for episodes within 28-days of randomisation (binary outcome) summarised by arm. As per section 5.1.

6.12 Secondary outcome – Clostridioides difficile infection

Outcome
Clostridioides difficile (C. difficile infection) within 28 days of randomisation. Defined as a positive laboratory test result for C. difficile toxin A and /or B tested on an unformed (diarrhoea) stool specimen.

Summary measure
Risk difference (difference in proportions) with 95% CI.

Analysis
The number and percentage (with 95% CI) of having at least one C. difficile infection for episodes within 28-days of randomisation (binary outcome) summarised by arm. As per section 5.1.

6.13 Secondary outcome – Antibiotic resistant infection

Outcome
Antibiotic resistant infection or colonisation within 28 days of randomisation.

Antibiotic resistant infection or colonisation is any of the following identified from sterile site culture (blood, urine, cerebrospinal fluid, peritoneal fluid, synovial fluid) or screening swab/stool:

- Methicillin-Resistant Staphylococcus aureus (MRSA): Staphylococcus aureus reported resistant to oxacillin
- Extended Spectrum Beta Lactamase-producing enterobacterales (ESBL): Escherichia coli, Klebsiella species., Enterobacter spp., Morganella spp., Providencia spp. or Proteus spp. in which a transmissible ESBL enzyme or plasmid-mediated AmpC has been reported.
- Carbapenemase-Producing Enterobacterales (CPE): Escherichia coli, Klebsiella species., Enterobacter spp., Morganella spp., Providencia spp. or Proteus spp. reported as resistant to meropenem
- Vancomycin Resistant Enterococci (VRE): Enterococcus faecalis or Enterococcus faecium reported resistant to vancomycin.
- Multidrug-resistant Pseudomonas aeruginosa (MRPAER): P. aeruginosa resistant to at least 2 or more of gentamicin, ciprofloxacin or a beta-lactams (e.g. piperacillin, ceftriaxone, ceftazidime, meropenem)

Summary measure
Risk difference (difference in proportions) with 95% CI.

Analysis
The number and percentage (with 95% CI) of episodes with at least one antibiotic-resistant infection/colonisation within 28-days of randomisation summarised by arm. As per section 5.1.

6.14 Secondary outcome – Clinician confidence and acceptability

Outcome
Clinician confidence and acceptability:
1. Number of episodes for which randomisation was overridden in STOP arm
2. Reason for continuing antibiotics in STOP arm:
   i) Presence of patient-specific risk factors;
   ii) Presence of clinically defined infection;
   iii) Clinical preference of treating oncologist;
   iv) Other reason

The number and percentage of episodes where randomisation was overridden in STOP arm will be given. The number and percentage of episodes with each override reason selected will be given.

6.15 Secondary outcome – Patient/parent/carer confidence and acceptability

Outcome
1. Number of participant episodes consented to study as proportion of eligible episodes
2. Number of participant episodes where randomisation was overridden in STOP arm due to withdrawn consent

The number and percentage (with 95% CI) of eligible patient episodes with a consent will be given. The number and percentage (with 95% CI) of STOP arm randomisation overridden due to withdrawn consent.

7. SAFETY OUTCOMES

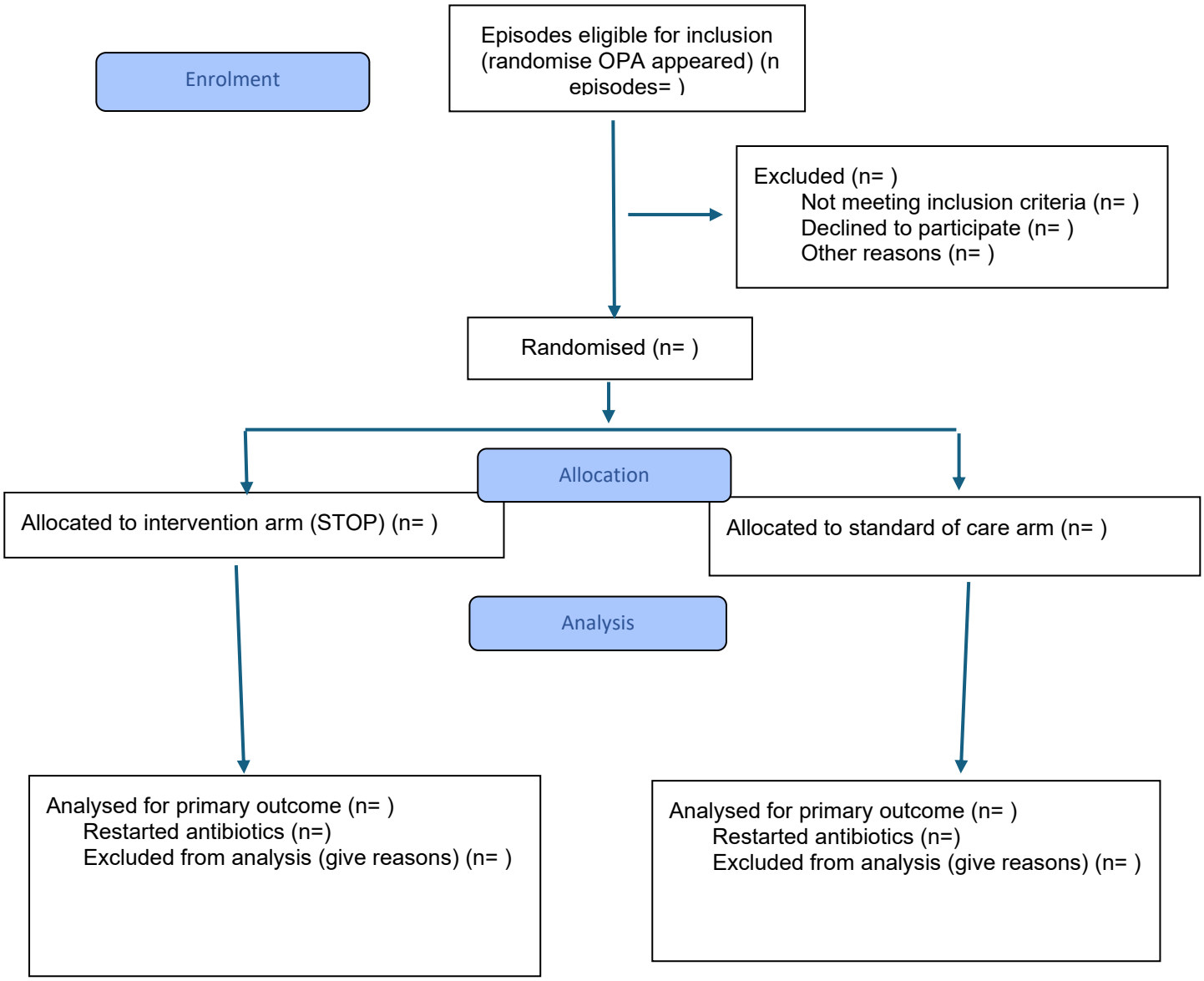
A listing of all reported adverse events will be presented. This will include adverse event type, grade, severity, relatedness, outcome, and treatment arm.

A summary of adverse event frequency by treatment arm and diagnosis type (ALL, AML, lymphoma, HCT) will also be presented (one by highest grade event only and if applicable all reported adverse events).

8. TABLES AND FIGURES

Figure 1: CONSORT 2025 Flow Diagram

Flow diagram of the progress through the phases of a randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis)



Listing 1: Reasons for declined consent or randomisation Epic alert

Alert type	Comment
Consent	Participant declined
Randomisation	Not clinically suitable

Table 1: Baseline Characteristics

	STOP arm	Standard of care arm	Total
Participant demographics			
Number of participants randomised	N(%)	N(%)	N
Number of febrile neutropenia episodes	N(%)	N(%)	N
Age at randomisation (years)	Mean(SD)	Mean(SD)	Mean(SD)
Sex (male, female, other)	Male (n%), Female(n%), Other (n%)	Male (n%), Female(n%), Other (n%)	Male (n%), Female(n%), Other (n%)
Disease type (type of leukaemia, lymphoma or HCT with underlying diagnosis)			
Treatment phase if ALL (induction, consolidation, maintenance)			
Days post-HCT at randomisation			
Central venous access (none, peripherally inserted central catheter, Hickman or portacath)			
Prescribed febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin)			
PJP Prophylaxis (TMP-SMX, dapsone, pentamidine)			
Antifungal prophylaxis in previous 7 days (amphotericin B, liposomal amphotericin, fluconazole, posaconazole, voriconazole, itraconazole, micafungin, caspofungin)			
Prescribed granulocyte colony stimulating factor (G-CSF) in previous 7 days			
Febrile neutropenia episode onset demographics			
Location at FN onset (outpatient or ward)			
Maximum documented temperature (within 4 hours of onset of FN)			
ANC at FN onset			
Fluid bolus (≥ 10 ml/kg volume) within 4 hours of FN onset			
Blood pressure below and/or heart rate above 95th percentile for age at time of randomisation			

**Footnote that unless specified all demographics are presented by participant episodes

Table 2: Compliance

	STOP arm	Standard of care arm
Number complaint episodes **footnote with definitions	N(%)	N(%)

Figure 2: Antibiotic and neutropenia durations

```
heatplot nday id2 rand_days, ylabel(,nolabels noticks) xlabel(-18(1)28,
labsize(vsmall)noticks angle(45)) xtitle("Days from randomisation")
color(white gs10) legend(label(1 "Neutropenic days"))  addplot(heatmap
anti id2 rand_days if anyday==1, legend(label(1 "STOP" 2 "SOC")))
graph export "$results\Graph.svg", as(svg) name("Graph") replace
```

Example below with random data
*Transparency and editing in inkspace-

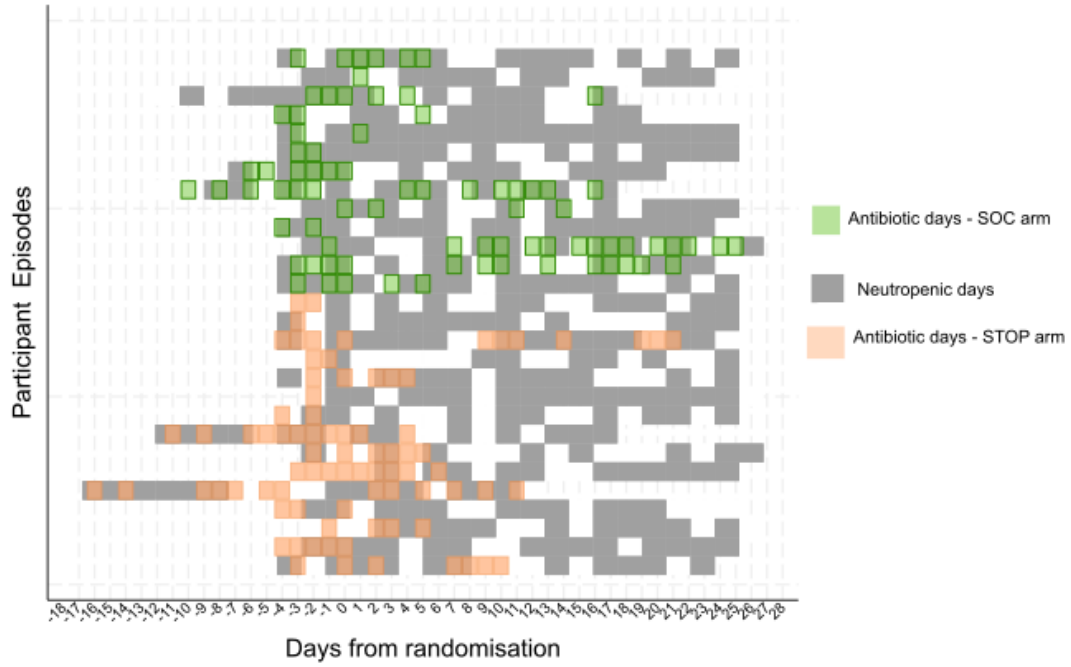


Figure 3: Histogram plot of antibiotic duration

Stata code

```
forvalues x=1/2 {
histogram DOT if arm==`x', freq saving(arm`x', replace) bin(5)
}

gr combine arm1.gph arm2.gph,col(1)
```

Example below with random data

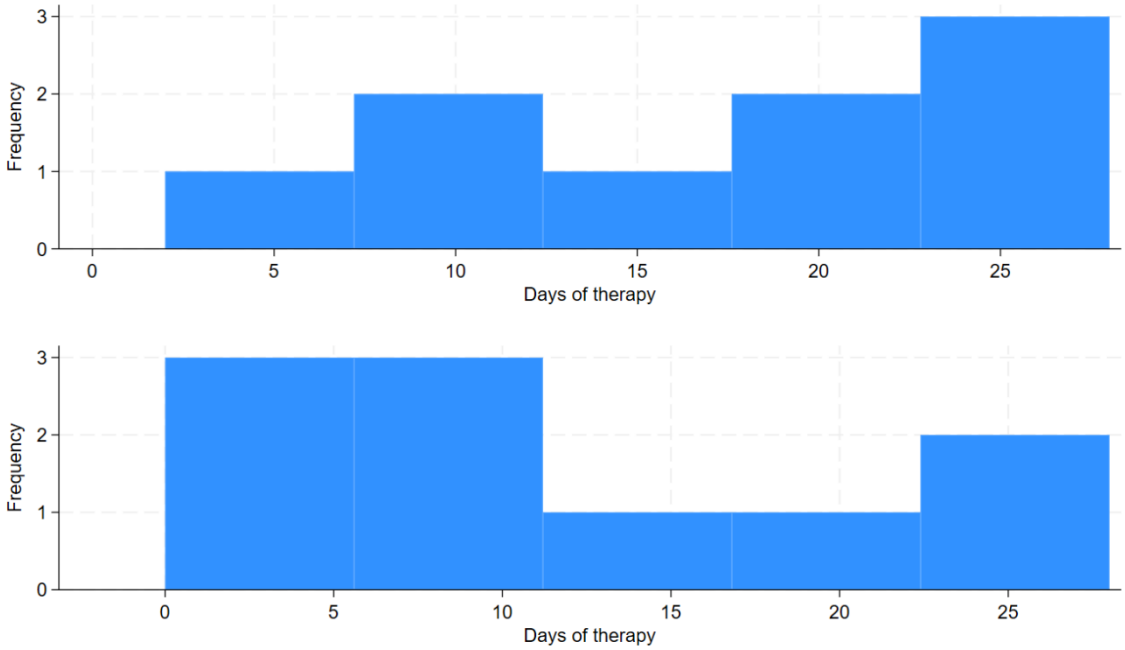


Table 3 : Concomitant therapies

	Medication	Arm(N%)	
Prescribed antibiotic prophylaxis in episode	Levofloxacin	STOP (n%)	SOC (n%)
	Ciprofloxacin		
	TMP-SMX		
	Other		
Antifungal prophylaxis	Fluconazole		
	Voriconazole		
	Other		
Granulocyte colony stimulating factor (G-CSF)			

Table 4: Primary Outcome - Percentage (95% CI) unfavourable clinical course

	Percentage episodes with unfavourable clinical course N (%) 95% CI		**Comparison between arms: Risk difference (95% CI)**
	STOP arm	**SOC arm**	

Table 5: Primary Outcome – Subgrouping of unfavourable clinical course by diagnosis

	Percentage episodes with unfavourable clinical course N (%)	
	STOP arm	**SOC arm**
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 6: Secondary Outcome 1.1 - Percentage (95% CI) of fever reoccurrence

	Percentage episodes with fever reoccurence (%) 95% CI		**Comparison between arms: Risk difference (95% CI)**
	STOP arm	**SOC arm**	
During same period of neutropenia			
Within 28 days of randomisation			

Table 7: Secondary Outcome 1.1 - Subgrouping of fever reoccurrence

	Percentage episodes with fever reoccurence N (%)	
	STOP arm	**SOC arm**
During same period of neutropenia		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		
Within 28 days of randomisation		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 8: Secondary Outcome 1.2 - Mean (95% CI) of duration of fever

	Mean duration of fever 95% CI		**Comparison between arms: Mean difference (95% CI)**
	STOP arm	**SOC arm**	
During same period of neutropenia			
Within 28 days of randomisation			

Table 9: Secondary Outcome 1.2 - Subgrouping of fever duration

	Mean duration of fever (SD)	
	STOP arm	**SOC arm**
During same period of neutropenia		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		
Within 28 days of randomisation		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 10: Secondary Outcome 2 - Percentage (95% CI) of febrile neutropenic episodes with at least one instance of clinical instability
Same as Table 6
Table 11: Secondary Outcome 2- Subgrouping of febrile neutropenic episodes with at least one instance of clinical instability
Same as Table 7

Table 12: Secondary Outcome 3 - Percentage (95% CI) of episodes with an ICU admission
Same as Table 6
Table 13: Secondary Outcome 3 - Subgrouping of episodes with an ICU admission
Same as Table 7

Table 14: Secondary Outcome 4 - Percentage (95% CI) of episodes with an ICU admission
Same as Table 6
Table 15: Secondary Outcome 4 - Subgrouping of episodes with an ICU admission
Same as Table 7

Table 16: Secondary Outcome 5 - Percentage (95% CI) of new positive blood culture within same period of neutropenia

	Percentage episodes with new blood culture (%) 95% CI		**Comparison between arms: Risk difference (95% CI)**
	STOP arm	**SOC arm**	

Table 17: Secondary Outcome 5 - Subgrouping of new positive blood culture within same period of neutropenia

	Percentage episodes with new blood culture (%)	
	STOP arm	**SOC arm**
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 18: Secondary Outcome 6 - Percentage (95% CI) of febrile neutropenic episodes with new infection

	Percentage episodes with new infection (%) 95% CI		**Comparison between arms: Risk difference (95% CI)**
	STOP arm	**SOC arm**	
Microbiologically defined infection (MDI)			
During same period of neutropenia			
Within 28 days of randomisation			
Clinically defined infection (CDI)			
During same period of neutropenia			
Within 28 days of randomisation			

Table 19: Secondary Outcome 6 - Subgrouping of febrile neutropenic episodes with new microbiologically defined infection (MDI)

	Percentage episodes with MDI N (%)	
	STOP arm	**SOC arm**
During same period of neutropenia		
Diagnosis type		
ALL		
AML		

Lymphoma		
HCT		
Within 28 days of randomisation		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 20: Secondary Outcome 6 - Subgrouping of febrile neutropenic episodes with new clinically defined infection (CDI)

	Percentage episodes with CDI N (%)	
	STOP arm	**SOC arm**
During same period of neutropenia		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		
Within 28 days of randomisation		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 21: Secondary Outcome 7 - Percentage (95% CI) of mortality

	Percentage episodes with mortality (%) 95% CI		**Comparison between arms: Risk difference (95% CI)**
	STOP arm	**SOC arm**	
All cause 28-day mortality			
Infection-related 28-day mortality (death with microbiologically proven or clinically suspected infection)			

Table 22: Secondary Outcome 7 - Subgrouping of episodes with mortality

	Percentage episodes with CDI N (%)	
	STOP arm	**SOC arm**
All cause 28-day mortality		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		
Infection-related 28-day mortality (death with microbiologically proven or clinically suspected infection)		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 23: Secondary Outcome 8 - Mean (95% CI) of duration of neutropenia

	Mean duration of neutropenia 95% CI		**Comparison between arms: Mean difference (95% CI)**
	STOP arm	**SOC arm**	

Table 24: Secondary Outcome 8 - Subgrouping of neutropenia duration

	Mean duration of neutropenia (SD)	
	STOP arm	**SOC arm**
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 24: Secondary Outcome 9.1 - Mean (95% CI) of duration of antibiotics

	Mean duration of antibiotics 95% CI		**Comparison between arms: Mean difference (95% CI)**
	STOP arm	**SOC arm**	
Length of therapy			
Days of therapy			

Table 25: Secondary Outcome 9.1 - Subgrouping of duration of antibiotics

	Mean duration of antibiotics (SD)	
	STOP arm	**SOC arm**
Length of therapy		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		
Days of therapy		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 26: Secondary Outcome 9.2 - Percentage (95% CI) of antibiotic reinstatement
Same as Table 16
Table 27: Secondary Outcome 9.2 - Subgrouping of antibiotic reinstatement
Same as Table 17

Table 28: Secondary Outcome 10 - Mean (95% CI) of total hospital length of stay

	Mean length of hospital stay 95% CI		**Comparison between arms: Mean difference (95% CI)**
	STOP arm	**SOC arm**	
Length in days of primary admission			
Total number of admitted days between randomisation and day 28			

Table 29: Secondary Outcome 10 - Subgrouping of hospital length of stay

	Mean duration of antibiotics (SD)	
	STOP arm	**SOC arm**
Length in days of primary admission		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		
Total number of admitted days between randomisation and day 28		
Diagnosis type		
ALL		
AML		
Lymphoma		
HCT		

Table 30: Secondary Outcome 11 - Percentage (95% CI) of unplanned readmission to hospital
Same as Table 16
Table 31: Secondary Outcome 11 - Subgrouping of unplanned readmission to hospital
Same as Table 17

Table 32: Secondary Outcome 12 - Percentage (95% CI) of C. difficile infection
Same as Table 16
Table 33: Secondary Outcome 12 - Subgrouping of C. difficile infection
Same as Table 17

Table 34: Secondary Outcome 13 - Percentage (95% CI) of antibiotic-resistant infection
Same as Table 16
Table 35: Secondary Outcome 13 - Subgrouping of antibiotic-resistant infection
Same as Table 17

Table 36: Secondary Outcome 13 - Clinician confidence and acceptability

Number of episodes for which randomisation was overridden in STOP arm	**N(%)**
Reason for continuing antibiotics	
Presence of patient-specific risk factors	n(%)
Presence of clinically defined infection	n(%)
Clinical preference of treating oncologist	n(%)
: list	n(%)

Table 37: Secondary Outcome 14 - Patient/parent/carer confidence and acceptability

	n/N
Number of participant episodes consented to study as proportion of eligible episodes	
Number of participant episodes where randomisation was overridden in STOP arm due to withdrawn consent	

Table 38: Summary of adverse events

	Trial arm		
	STOP arm	**SOC arm**	**Total**
Adverse event	N	N	N
Adverse event type	n	n	n
Bacteraemia	n	n	n
etc			

Listing 2: Adverse Events

Study ID	Adverse Event	Grade	Severity	Relatedness	Outcome	Trial arm
XX	Bacteraemia	1/5	Serious (Y/N)	Related (Possibly/Unlikely/Unrelated)	Resolved/ongoing	STOP/SOC

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4. Blanche.P, Vissing.NH, & Ulrikka Nygaard,U. Jan 2025. Statistical Analysis Plan (SAP): Early termination of empirical antibiotics in febrile neutropenia in children with cancer. https://cdn.clinicaltrials.gov/large-docs/64/NCT04637464/SAP_000.pdf

APPENDIX A. CLINICAL INSTABILITY VICTOR CHARTS

Victorian Children's Tool for Observation and Response (VICTOR) charts as of OCT2021
Please see https://www.rch.org.au/educationhub/Education_resources/ViCTOR/ for current documents

All values in Clinical Review (CR) Criteria can be assumed to be inclusive unless included in the MET critera. eg. a respiratory rate of 25 breaths/min in a 2 mth old is a CR, but 20 breaths/min is a MET.

Observation	Criteria (MET/CRC)	Age	Result
Level of Consciousness	MET criteria	All Ages	Unresponsive
Respiratory Rate (breaths/min)	MET criteria	< 3 mths	≤20; ≥75
	CR criteria	< 3 mths	20-25; 60-75
	MET criteria	3-12 mths	≤20; ≥70
	CR criteria	3-12 mths	20-25;55-70
	MET criteria	1-4 yrs	≤16; ≥56
	CR criteria	1-4 yrs	16-20;40-56
	MET criteria	5-11 yrs	≤13; ≥46
	CR criteria	5-11 yrs	34-46;13-16
	MET criteria	12-18 yrs	≤10; ≥34
	CR criteria	12-18 yrs	10-14;26-34
O2 Saturation (%)	MET criteria	< 3 mths	≤89
	CR criteria	< 3 mths	90-93
	MET criteria	3-12 mths	≤89
	CR criteria	3-12 mths	90-93
	MET criteria	1-4 yrs	≤89
	CR criteria	1-4 yrs	90-93
	MET criteria	5-11 yrs	≤89
	CR criteria	5-11 yrs	90-93
	MET criteria	12-18 yrs	≤89
	CR criteria	12-18 yrs	90-93
Heart Rate (beats/min)	MET criteria	< 3 mths	≤100;≥185
	CR criteria	< 3 mths	100-110;170-185
	MET criteria	3-12 mths	≤95;≥180
	CR criteria	3-12 mths	165-180;95-105
	MET criteria	1-4 yrs	≤75;≥165
	CR criteria	1-4 yrs	75-85;150-165
	MET criteria	5-11 yrs	≤60;≥150
	CR criteria	5-11 yrs	60-70;135-150

MET criteria	12-18 yrs	≤50;≥135
CR criteria	12-18 yrs	50-60;120-135

Systolic Blood Pressure (mmHg)		
MET criteria	< 3 mths	≤60
CR criteria	< 3 mths	≥105
MET criteria	3-12 mths	≤65
CR criteria	3-12 mths	≥115
MET criteria	1-4 yrs	≤70
CR criteria	1-4 yrs	≥120
MET criteria	5-11 yrs	≤80
CR criteria	5-11 yrs	≥130
MET criteria	12-18 yrs	≤95
CR criteria	12-18 yrs	≥140