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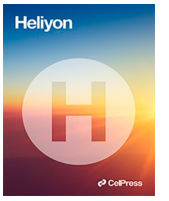

Research article

Early stoppage of empirical antibiotic therapy at clinical improvement in paediatric leukaemia patients with high-risk febrile neutropenia (ESAT-HR-FN study): Study protocol of a single centre investigator initiated randomised open label non-inferiority trial

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A B S T R A C T

Background and rationale: Febrile neutropenia (FN) is one of the major causes of early mortality among children undergoing induction chemotherapy for haematological malignancies. FN occurs in up to 80 % of the children undergoing intensive chemotherapy and FN specific mortality is as high as 10 %. The management of high-risk FN (HR-FN) is by early initiation of broad-spectrum empirical antibiotic therapy (EAT) which is continued till blood count recovery. Adverse effects of prolonged EAT among children without proven infective focus have questioned the rationale behind the duration of EAT. The non inferiority of early stoppage of EAT in patients with low-risk FN (LR-FN) when afebrile for 48 h, irrespective of marrow recovery, is proven among adults and children. However, there is paucity of data regarding the same in children with HR-FN. This study aims to determine whether early discontinuation of EAT in children with HR-FN without proven infective focus who become afebrile and awaiting marrow recovery, would reduce antibiotic duration and their adverse effects without any negative consequences for patients.
Objective: To compare the rates of recurrent fever in paediatric patients (2–18 years) with HR-FN when EAT is continued till marrow recovery (control group) versus when stopped early at defervescence irrespective of marrow recovery (study group).
Methodology: This is the study protocol of a phase 3, single centre, randomized, open label, non-inferiority clinical trial. The primary outcome is the rate of fever recurrence among patients with HR-FN, when EAT is stopped early irrespective of marrow recovery (study group) and will be compared to the rate of fever recurrence on continuation of EAT till marrow recovery which is defined as an absolute neutrophil count (ANC) $\geq$ 500/mm^3 (control group). Secondary outcomes include the comparison of duration of antibiotic use, mortality rates, hospital re-admission rates, requirement of multiple broad-spectrum antibiotics, therapeutic anti-fungal usage and need for organ support between the study and the control groups. A total of 280 children with acute leukaemia undergoing EAT for grade 3 or severe FN (ANC <500/μL) without clinico-laboratory evidence of infective foci are being randomized in the ratio of 1:1 between the study and the control group after defervescence for 48 h. The patients will be followed up for primary outcome (fever recurrence) till the end of induction period (day 35) or recovery of ANC $\geq$500/mm^3 whichever is earlier.
Expected outcome: ESAT-HR FN study is the first large phase 3 randomised study to assess the impact of early stoppage of EAT irrespective of marrow recovery among a homogenous paediatric cohort of HR-FN in the setting of induction chemotherapy for acute leukaemia. This study will be seminal in addressing the duration of EAT in HR-FN among children without infective foci and if proven to be non-inferior this strategy will help to reduce the adverse effects from prolonged antibiotic use, the emergence of drug resistance, decrease hospital stay length and overall health care costs.

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1. Introduction

In children with haematological malignancies undergoing induction chemotherapy, the resultant neutropenia and subsequent febrile illness has been the major cause of early mortality. Febrile neutropenia (FN) occurs in around 10%–50 % of patients with solid tumours with rates as high as 80 % with hematologic malignancies receiving one or more chemotherapy cycle(s), with resultant FN specific mortality reaching up to 10 percent [1]. The magnitude of inflammatory response is attenuated among neutropenic patients and first febrile episode may be harbinger of a serious underlying infection. Early initiation of broad-spectrum intravenous antibiotics while awaiting detailed evaluation of aetiology for a febrile episode has been shown to decrease the serious infection related complications and death [2]. Blood stream infection is the most common form of documented aetiology for FN [3,3]. Catheter related coagulase-negative staphylococci (CoNS) are frequently isolated bacteria in the Western countries, whereas multidrug-resistant gram-negative bacteria (MDR-GNB) species predominate in the developing countries. In addition, resistant gram-positive pathogens, such as methicillin resistant staphylococcus aureus (MRSA) and vancomycin resistant enterococci (VRE), have become more common and are the most prevalent resistant isolates in some centres, accounting for 20 % and more because of absence of antibiotic stewardships [4–6]. Also, tropical organisms and viral aetiologies needs to suspected as a cause for febrile neutropenia other than bacteria when cultures are sterile [7–13]. The aetiology for FN remains unidentified in most of the cases [14]. Empirical antibiotic therapy (EAT) is commonly continued till recovery of neutrophil counts, even with the clinical recovery of patients and no documentation of any infective focus.

Due to uncertainty of aetiology, clinical severity, and potential adverse consequences of EAT among patients with FN, risk stratification at presentation remains the central dogma for treatment of chemotherapy induced FN [15]. Multinational Association for Supportive Care in Cancer score (MASCC), or Clinical Index of Stable Febrile Neutropenia (CISNE) scoring are used as risk stratification scores, which are not optimal for stratifying ultra-high-risk adult patients especially when presented with impending organ failure and MASCC is favoured over CISNE in triaging adult patients with FN in emergency [16]. Studies of risk prediction in children include retrospective and prospective observational cohort studies that vary in inclusion criteria, specific definitions of FN, and exact outcomes measured [17]. The process of deriving prediction rules frequently overestimates their effectiveness in practice and the rules require geographic and temporal validation [18,19]. Supplementary Table S1 summarizes the current risk stratification strategies for FN in children.

Among low-risk FN (LR-FN), outpatient oral antibiotic policy and early discontinuation of antibiotics at clinical improvement before marrow recovery have been proven to be equally efficacious and non-inferior to in-patient and prolonged intravenous antibiotic policy till marrow recovery in both adults and children [13,17,20–26]. Among adult patients with high-risk FN (HR-FN), a large multicentre, open label, non-inferiority randomised controlled trial from Netherlands has already demonstrated that stoppage of antibiotics at defervescence without marrow recovery is feasible [27]. However, there is no robust data in children with HR-FN for early stoppage of EAT. A prospective multi-centre randomised study in children with either HR-FN or LR-FN who tested positive for respiratory viral pathogen, when afebrile on antibiotics at 48 h were randomised between early stoppage versus continuation of antibiotics till marrow recovery and it proved non inferiority of early stoppage strategy [28]. However, persistence of virus after clinical recovery, asymptomatic colonization, and other factors questions the implementation of routine testing for virus prior to early stoppage of antibiotics. In a recently conducted systematic review including studies on both adults and children (3 studies included

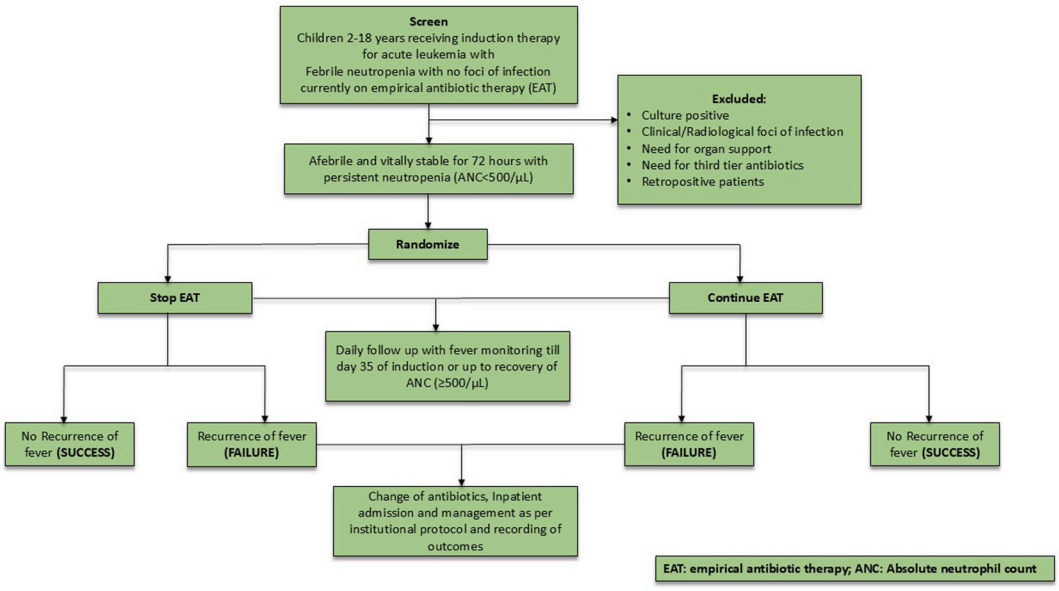

Fig. 1. Flow of the study.

only children) addressing the question of early stoppage of EAT showed that with a shortened antibiotic course there is no difference in mortality, recurrent fever rate, severe infections and hospitalisation, although studies were heterogenous [29]. Supplementary Table S2 summarizes the available evidence supporting or refuting the strategy of early stoppage of EAT at defervescence for FN [23,27,30–36].

Based on current available evidence, it remains unclear whether early stoppage of EAT is a feasible and non-inferior strategy among children with HR-FN at defervescence without any clinical focus of infection. This study describes the clinical trial protocol of ESAT-HR FN study assessing the non-inferiority of early stoppage of EAT compared to continuation of EAT till marrow recovery. The trial protocol is as per the specifications of the SPIRIT statement 2013 version 1.1 (Supplementary Table S3). [37,38].

2. Methods/design

2.1. Study design

ESAT-HR FN is an investigator initiated single centre open label non inferiority study addressing the effectiveness of early stoppage of empirical antibiotics in children with HR-FN during induction chemotherapy for acute leukaemia. The trial protocol has been approved by the institutional ethics committee at All India Institute of Medical Sciences, New Delhi (IECPG-424/September 27, 2018). The trial was conducted according to Declaration of Helsinki and good clinical practices guidelines. The trial was registered in Clinical Trials Registry of India, CTRI/2018/015994. The study flow has been summarised in Fig. 1. There was no involvement of patient, their families or representatives in the design of the study.

2.2. Objectives

i. Primary Objective

To compare the rates of recurrent fever in children (2–18 years) with high-risk febrile neutropenia (HR-FN) between study and control groups.

ii. Secondary Objectives

- To compare the duration of antibiotics in children (2–18 years) with HR FN between the control and study groups.
- To compare the mortality rates in children (2–18 years) with HR-FN between the control and study groups.
- To compare the rates hospital re-admission in children (2–18 years) with HR-FN between the control and study groups.
- To compare the requirement of third line antibiotics and therapeutic anti-fungal in children (2–18 years) with HR-FN between the control and study groups.
- To study the role of procalcitonin in de-escalation of antibiotics in children (2–18 years) with HR-FN.

2.3. Study population

This study is being conducted among children of acute leukaemia undergoing induction treatment at the in-patient wards and out-patient clinics of Department of Medical Oncology at the Dr. BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, a central government-funded tertiary care cancer hospital. It caters to a population of over 20 million people and has a catchment area including states of Delhi, Uttar Pradesh, Haryana, Bihar, Rajasthan, Punjab and Madhya Pradesh.

2.4. Inclusion criteria

The participants should fulfil all the inclusion criteria prior to enrolment:

- Age above or equal to 2 years and below or equal to 18 years.
- Patients diagnosed with therapy naïve or relapsed Acute myeloid leukaemia (AML) or Acute lymphoblastic leukaemia (ALL) and having febrile neutropenia during induction chemotherapy (Supplementary Table S4).
- Blood cultures taken before or within 24 h of starting antimicrobial treatment.
- Children 2–7 years whose parents/legally authorized representative give written informed consent, children 8–18 years who give assent along with written informed consent by parents/legally authorized representative.
- Clinically infection free and afebrile for 72 h on intravenous antibiotics.

2.5. Exclusion criteria

Participants fulfilling any of the below mentioned criteria are excluded from the study.

- Already enrolled in the study during previous febrile neutropenia episode.
- Children positive for Human immune-deficiency (HIV) serology.
- Patients on third line antibiotics as per institutional protocol (Supplementary Table S4)

- Patients who required therapeutic antifungals during screening period.
- Patient who requires any type of organ support during treatment of febrile neutropenia (Inotropic support/Mechanical ventilation/haemodialysis).
- Severe renal function impairment defined as creatinine clearance less than 30 ml/min.
- Clinical foci of infection (Pneumonia/Gastroenteritis including necrotising enterocolitis/Urinary tract infection/Soft tissue infection/Meningitis) as per treating physicians' assessment.
- Radiological foci of infection as reported by consulting radiologist (Xray chest/Computed tomographic scan of chest or abdomen or by ultrasonographic scan of abdomen)
- Microbiologic evidence of infection evaluated as per clinical symptoms (Culture/staining/Polymerase chain reaction-based test(s) positive for infectious organism on body fluids like blood, urine, sputum, or cerebrospinal fluid)
- Patient who had undergone hematopoietic stem cell transplant.
- Patient diagnosed as mixed phenotypic acute leukaemia, acute promyelocytic leukaemia, Blastic plasmacytoid dendritic cell neoplasm or Burkitt's leukaemia.

2.6. Recruitment

All children 2–18 years who develops FN during induction therapy for acute leukaemia are screened universally for ESAT HR-FN trial eligibility. Patients with upfront ALL are treated as per ICiCLE-ALL-14 (Indian Collaborative Childhood Leukaemia group) protocol, while those with relapsed ALL with Medical Research Council UK-ALLR1 protocol or Berlin-Frankfurt-Munster (BFM) 90 protocols on outpatient/daycare basis at our institute [39–41]. Children with upfront AML are treated with AD (Cytosine arabinoside, Daunorubicin) protocol as inpatient or ADE induction (Cytosine arabinoside, Daunorubicin, Etoposide) on outpatient basis. Children with relapsed AML are treated as per ADE induction. Outpatient regimen is proved equally efficacy without increase in adverse events [42,43].

Any child who develops first episode of FN during induction chemotherapy for acute leukaemia, is evaluated for possible aetiology and possible infective foci (aerobic blood cultures within 24 h of fever onset, hemogram, renal and liver function tests, chest radiograph, cerebrospinal fluid analysis if clinical suspicion of meningitis, and urine cultures if symptomatic, ultrasonogram of abdomen-pelvis if clinical neutropenic enterocolitis). EAT is initiated as per institutional protocol on dual antibiotics with at least one anti-pseudomonas agent (Supplementary Table S5). Upfront MRSA-coverage are used only in select cases (Supplementary Table S5). Surveillance cultures for colonization by antibiotic-resistant bacteria are not routinely practised [44]. Children are treated uniformly as an in-patient in case of haemodynamic instability, need for organ support or necessitating prolonged infusion medications (third-line antibiotics, Table S4), otherwise the same intravenous antibiotics are administered on outpatient/daycare basis for patients with stable vitals. These subjects are followed alternate day with complete hemogram along with fever monitoring and antibiotic escalation as per institutional protocol in presence of fever (Supplementary Table S4). Children who becomes afebrile for 72 h on EAT with persistent neutropenia {absolute neutrophil count (ANC) $< 500/\mu L$}and without any clinical/radiological foci of infection are screened for ESAT-HR FN study. On fever recurrence, antibiotics were restarted uniformly across both groups as per clinical indication.

During this screening time, children and caregivers are provided written and verbal information about the clinical trial in their own understandable language. Once an eligible subject is screened, consent is taken from caregiver prior to enrolment in the study and randomisation. Signed consent and assents (where applicable) are obtained by designed clinical staff (study nurse) assigned to this responsibility. Informed consent is obtained from the parents of patients or from the authorized surrogates. Assent is obtained in children $\geq$7 years old.

Recruitment in the study was initially planned over 36 months but got significantly delayed due to coronavirus disease-19 pandemic and is expected to complete in six years of the initiation of the study. The study is currently ongoing at the institute and has completed recruitment of 268 patients (95 %) as of December 2023.

2.7. Randomisation

A permuted stratified block randomisation strategy is followed with variable block size [4–8], stratified for type of leukaemia (AML, ALL and relapsed acute leukaemia), using random sequence generated from Random Lists (www.randomlists.com). Study participants are allocated 1:1 between the two study groups. For maintaining allocation concealment, randomisation is being done by a research officer who is not actively involved in the patient recruitment or recording study outcomes. Once randomized, the clinician/study nurse obtains the treatment allocation for that patient and communicate to treating physician.

2.8. Intervention

For the experimental group (antibiotic stop group), EAT is discontinued when the patient remains afebrile, with resolution of signs, symptoms, and normalization of vital signs for $\geq$72 h with ANC $<500/\mu L$ (irrespective of ANC count). For the Control group (Antibiotic continuation group), EAT is discontinued only when the patient is afebrile, with resolution of signs, symptoms, and normalization of vital signs for $\geq$72 h along with recovery of ANC (defined as $\geq 500/\mu L$). Use of prophylactic antifungals, antivirals, and *Pneumocystis carinii* pneumonia prophylaxis are allowed as per induction protocols and are continued during study period. No prophylactic gram positive or gram-negative antibiotics are allowed during the study period. Growth factors use {Granulocyte colony stimulating factor (GCSF) or Pegylated-GCSF) is allowed on subject to subject basis at the decision of treating physician. The dose and duration of G-CSF/

Peg G-CSF (if used) is noted. Blood product transfusions are allowed throughout the study period to maintain haemoglobin above 7 g/dL and platelet count above 20000/μL during febrile episodes or clinical bleeding, and above 10000/μL otherwise.

2.9. Choice of comparator

The standard of care till date for HR-FN among children is to continue EAT till marrow recovery which is defined as ANC >500/μL in patients who have no clinical or laboratory evidence of bacterial infection [26]. Hence, continuation of EAT till marrow recovery was considered as a comparator group.

2.10. Study endpoint

After randomisation, patients are followed up daily for primary and secondary objectives until day 35 of induction or till recovery of ANC ≥500/μL whichever is earlier. With completion of induction and marrow recovery risk of FN drops significantly till consolidation chemotherapy and consequent neutropenia. As percurrent guidelines antibiotics antibiotics are stopped at marrow recovery and afebrile period of 48 h. Trial patients being randomised at afebrile period and fever recurrence being primary outcome, follow up period till end of induction or marrow recovery is clinically meaningful.

3. Rationale for choice of outcome measurement

EAT is commonly continued till marrow recovery to maintain persistent exposure of antibiotics to clear bacteraemia in a severely neutropenic patient, even without any apparent fever. The recurrence of fever due to stoppage of EAT signifies recrudescence of bacteraemia or antibiotic resistance signifying failure of the strategy. The fever recurrence is the first clinically measurable consequence of antibiotic failure, sepsis and multiorgan dysfunction. Hence the fever recurrence is considered in this study as the primary outcome, which is clinically meaningful and easily measurable parameter. Febrile neutropenia subjects during leukaemia chemotherapy induction have multiple confounding factors for monitoring specific adverse effects from antibiotic regimen like multiagent chemotherapy modified as per toxicity, ongoing febrile illness and overlapping multiple antibiotics Though subclinical or less than grade 3 antibiotic specific adverse effects are not captured as secondary outcome, clinical consequences are monitored and will be analysed.

4. Outcome

The outcomes for this study include:

4.1. Primary outcome

- The rate of fever recurrence in experimental group (early stoppage of EAT irrespective of marrow recovery) compared to control group (continuation of EAT till marrow recovery) in children with HR-FN episodes.

4.2. Secondary outcomes

- The duration of EAT in experimental group (early stoppage of empirical antibiotics irrespective of marrow recovery) compared to control group (continuation of antibiotics till marrow recovery) among children (age 2–18 years) with HR-FN.
- The mortality rates in experimental group (early stoppage of empirical antibiotics irrespective of marrow recovery) compared to control arm (continuation of antibiotics till marrow recovery) among children (2–18 years) with HR-FN.
- The rates of hospital re-admission in experimental group (early stoppage of empirical antibiotics irrespective of marrow recovery) compared to control group (continuation of antibiotics till marrow recovery) among children (age 2–18 years) with HR-FN.
- The requirement of third tier antibiotics (defined as Supplementary Table S4) and therapeutic anti-fungal in experimental group (early stoppage of empirical antibiotics irrespective of marrow recovery) compared to control group (continuation of antibiotics till marrow recovery) among children (2–18 years) with HR-FN.
- To study role of procalcitonin in de-escalation of antibiotics in children (2–18 years) with HR-FN.

5. Follow up

The subjects in either group is clinically followed daily with regular temperature monitoring. (six hourly temperature charts) on outpatient basis (Supplementary Table S6). In case of fever recurrence, antibiotics are re-initiated if randomised to stop group or changed if randomised to continuation group along with taking repeat blood cultures or any other laboratory investigations as per the need of clinical status and patients are managed as per standard of care. After randomisation admission policies are uniform across trial groups which include need for prolonged infusion antibiotics, need for 3 tier antibiotics, organ support etc. Patients admitted in hospital are monitored for fever every 4 h, while for outpatients, patients self-monitor for fever with objective documentation of temperature in a pre-designed patient diary (Supplementary Table S6) along with daily physical or telephonic reinforcement by study team. Adherence to antibiotics and laboratory investigations (complete blood count) as per protocol is ensured by every alternate day

physical follow-ups and daily telephonic consultations as per convenience of the patients. The timeline of various assessments from enrolment to follow-up is summarised in SPIRIT timeline as in Table 1. Subjects who have recurrent fever are initiated on EAT as per institutional protocol and also evaluated for fungal and viral aetiologies which are documented.

6. Safety

All adverse events reported in the trial have been discussed twice among the departmental faculty not involved in the trial for the assessment of causation by the intervention at an open forum and no death is reported to be caused by the intervention. Any death of subjects recruited after the presentation will be reviewed by the same team and if present will be reported timely to institutional ethics committee. Participants are free to withdraw consents at any point of the study and standard of care will not be compromised for the same. Ancillary and post-trial care would continue for both the arms of the study as per disease specific protocols or institutional standard of care.

7. Statistical considerations

7.1. Sample size

A clinical audit conducted over a period of 2 months at the authors' institute among children with HR-FN undergoing induction chemotherapy for acute leukaemia, prior to initiation of the study. The fever recurrence rate was found to be 36 % among the patients who were given antibiotics till marrow recovery defined as ANC) ≥500/μL. A local prospective clinical audit was preferred for sample size calculation to get a more accurate reflection of infection burden at the local setting. Considering a non-inferiority margin of 15 %, total 125 patients is needed to recruit in each arm to demonstrate non-inferiority of the experimental strategy, with one sided alpha error of 5 % and 80 % power. The non-inferiority margin of 15 % for primary endpoint of fever recurrence was chosen based on the assumption that it translates into an acceptable increase in proportion of clinically meaningful serious medical complication by 3–5% based on previous prospective studies [36,45]. Accounting for 10 % attrition/loss-to-follow-up, total 280 patients (140/group) were planned to be recruited to address the primary end point of fever recurrence. The recruitment was planned over 3 years, however, in view of slowdown of recruitment due to coronavirus disease-19 pandemic in the intervening years, the accrual is likely to be completed by August 2024.

Table 1
Participant timeline for assessment of events (SPIRIT Table).

	STUDY PERIOD							
	Screening	Allocation	Post-allocation					Close-out
TIMEPOINT**	***D-3***	**D0**	***D1***	***D2***	***D3***	***D4***	***D5 …***	***Day 35 of induction or count recovery (whichever is earlier)***
ENROLMENT:	**D1-D35 of induction period for episode of neutropenic fever**	**When afebrile for 72 h, no clinical foci and ANC<500**						
Eligibility screen	XX							
Informed consent		XX Screening just prior to randomisation						
Hemogram, Renal and liver function tests, Blood cultures (must), Other body fluid cultures, Imaging on individual patient basis	XX							
Randomisation and masked Allocation		X						
INTERVENTIONS								
Experimental Arm: Stoppage of antibiotics			X					
Control Arm: Continuation of antibiotics			X					
ASSESSMENTS								
Fever recurrence			X	X	X	X		
Hemogram, Renal and Liver function tests				X		X		
Use of growth factors			X	X	X	X	X	
Use of blood products								
Intravenous antibiotics used and duration of use			X	X	X	X	X	
Need for hospital admission and days of hospital admission			X	X	X	X	X	
Need for organ support (Oxygen, inotrope requirement)			X	X	X	X	X	
Final outcome								X

7.2. Statistical analysis plan

Descriptive statistics will be used to summarize the demographic and clinical characteristics of the subjects. For primary objective, the absolute difference in the rates of fever recurrence between the two groups with two-sided 90 % confidence intervals will be estimated to assess the lower limit of one-sided 95 % CI. Non-inferiority will be claimed if lower limit of one-sided 95 % CI does not exceed 15 %. Secondary objectives will be compared for absolute and relative benefits with 95 % CI. The results of logistic regression will be expressed by odds ratio (OR), 95 % Confidence Interval (CI). Subgroup analysis for stratified groups will be done, although the sample size is not powered for stratified subgroups. Regression models (including but not limited to linear, logistic, or proportional hazards models) will be used for exploratory analyses. All analyses will include every randomized patient and be conducted using the intention-to-treat principle analysing according to randomized treatment regardless of treatment received. Additionally, per-protocol analyses will be carried out for the study population based on actual intervention received.

8. Data processing, auditing, storage and dissemination

Individual case record forms (CRF) containing different items dealing with demographic and clinical characteristics of the subjects are being used. Patients' hospital records are reviewed and telephonic communication with parents are used for capture of any missing data. Separate files are allocated to each patient to store the trial data. All procedures for the handling and analysis of data are conducted using good computing practices meeting institutional guidelines for the handling and analysis of data for clinical trials. The collected data is anonymized, and confidentiality is maintained by allotting unique trial number to participant and collection or management of data is done with reference to this unique number. Consent forms (with identifying data of patients) and Case record forms are kept in locked compartments at the study site that can exclusively be accessed by authorized personnel only.

A separate external data monitoring committee (DMC) or trial steering committee was not constituted. The principal investigator at the All-India Institute of Medical Sciences, New Delhi, is coordinating the study and be responsible for data acquisition and management and statistical analysis. Data will be presented to senior faculty not involved in the trial in the department at regular intervals, currently it has been presented twice at the time of publication of this protocol. Additionally, the data is open for audit or inspection by the institutional ethics committee. The results of the trial are planned to be disseminated by presentation in national/international conferences as well as by publication in a peer-reviewed journal.

9. Discussion

For microbiologically or clinically documented infection, there is un-equivocal evidence regarding duration of antibiotics for at least 7–10 days [26]. In a child presenting with chemotherapy induced FN, the probability of identifying a causative microorganism ranges only between 10 and 40 % [46]. Most FN patients have unidentified aetiology for FN and are being treated with prolonged duration of empirical broad spectrum of antibiotics till marrow recovery which is arbitrarily defined as ANC $\geq$500/μL. The cause of fever in these subsets of patients of FN are varied and include viral fever syndromes, hemophagocytic lympho-histiocytosis, drug induced, and malignancy induced fever [47]. Most of these aetiologies are not distinguishable clinically and hence, most of the children end up being treated with prolonged duration of antibiotics. However, prolonged use of broad-spectrum antibiotics in patients with FN has been linked to multiple adverse effects including the increase in incidence of multi-drug resistance (MDR) organisms, *Clostridium difficile* associated diarrhoea and invasive candidiasis [48,49]. Multi-drug resistance especially carbapenem resistance is associated with 5-fold increase in mortality [50–52]. Prolonged antibiotics also alters anaerobic gut microbiota and increases the risk of induction mortality and graft versus host disease (GVHD) during stem cell transplantation [53,54]. Additionally, this results increased costs of treatment and unnecessary healthcare resource utilization.

Due to absence of level 1 evidence, various guidelines have heterogenous recommendations, largely based on retrospective data and expert consensus. Guidelines from American society of clinical oncology (ASCO) published in 2017, Infectious disease society of America (IDSA), in its update in 2010 and European society of clinical oncology (ESMO) suggests a discontinuation of EAT after the marrow recovery and an afebrile period for 24–48 h in high-risk adult patients [46,55]. In addition, ECIL-4 (European conference on infections in leukaemia −4) recommends early discontinuation of EAT irrespective of risk category/marrow recovery among both adults and children and UK-NICE 2013 guidelines also recommend early discontinuation of EAT among high-risk febrile neutropenic adults irrespective of marrow recovery [56,57].

In contrast to adults, the evidence is sparse in paediatric population. The 2023 updated guidelines on children with FN have raised a knowledge gap in early stoppage of EAT in HR-FN with unknown origin during neutropenia which emphasizes the need for a high-quality RCT [25]. The demonstration of non-inferiority of the strategy of early stoppage of EAT independent of marrow recovery, would decrease prolonged use of antibiotics reducing its adverse consequences.

The ESAT-HR-FN trial addresses the stoppage of EAT in a large homogenous paediatric patient with FN during acute leukaemia induction, a high-risk subset in real world scenario in a randomised fashion. The patients are prospectively followed for fever recurrence, along with prospective record of outcomes which are the advantages of the study. Even though, the study follows stratified randomisation based on type of leukaemia (AML, ALL and relapsed leukaemia), it is not powered for individual subgroups. Additionally, use of biomarkers like detection of bacterial DNA in blood or inflammatory markers may help in identification of cases where strategy of early of EAT is prudent [58,59]. This study does not explore various biomarkers, which limits the potential selection of subgroup which benefits the most from the strategy of early stoppage of antibiotics regardless of marrow recovery in patients with HR-FN [60,61]. Furthermore, adverse effects, specifically due to prolonged antibiotics, are not being prospectively monitored in the

trial, and in absence of causality assessment, the difference of adverse effects between the two groups with respect to antibiotic use cannot be ascertained. The results of the trial will be valuable in real-world clinical decision-making regarding stoppage of EAT in high-risk paediatric febrile neutropenia.

Clinical trials registration details

Clinical Trials Registry of India, CTRI/2018/015994; Trial Registration Date: October 10, 2018; Amendment to protocol: None.

Funding

The trial is the investigator-initiated trial and do not receive any specific funding. The infrastructure, logistic and administrative support is provided by All India Institute of Medical Sciences, New Delhi where the study is conducted.

Data availability statement

No data was used for the research described in the article.

Ethics declaration

The trial protocol has been approved by the institutional ethics committee at All India Institute of Medical Sciences, New Delhi (IECPG-424/September 27, 2018). The trial was conducted according to Declaration of Helsinki and good clinical practices guidelines. Written informed consent was taken from parent/primary caregiver of all screened children and assent was taken from all children >7 years of age.

CRediT authorship contribution statement

Santhosh Kumar Kn: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology. **Santhosh Kumar Chellapuram:** Visualization, Project administration, Methodology, Conceptualization. **Shuvadeep Ganguly:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Data curation. **Deepam Pushpam:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Conceptualization. **Rupak Kumar Giri:** Resources, Project administration, Methodology, Investigation. **Sameer Bakhshi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36310.

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