39·0°C versus 38·5°C ear temperature as fever limit in neutropenic children with chemotherapy for cancer: a multicentre, randomised, non-inferiority trial.

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ABSTRACT

Background. Fever in neutropenia (FN) is the most frequent complication of chemotherapy for cancer. The temperature limit defining fever used clinically varies. A higher limit can avoid unnecessary FN diagnoses in patients spontaneously recovering from fever. This trial primarily aimed to determine if a limit of 39·0°C ear temperature is non-inferior to 38·5°C regarding safety.

Methods. This prospective controlled non-blinded multicentre trial repeatedly randomised paediatric cancer patients in monthly clusters to limits of 39·0°C or 38·5°C ear temperature. FN diagnosis below the randomised limit was allowed for clinical reasons. The primary outcome was the rate of FN with safety relevant events (SRE) per chemotherapy year. This trial is registered at ClinicalTrials.gov, number NCT02324231.

Findings. Six centres recruited 269 patients until the trial was stopped for success after the second interim analysis. A SRE was diagnosed in 72 (20%) of 360 FN episodes (death, 0; intensive care unit admission, 16; severe sepsis, 22; bacteraemia, 56). In 92 chemotherapy years randomised to 39·0°C, 151 FN episodes were diagnosed (1·64/year), including 22 (15%) with SRE (0·24/year). In 103 years randomised to 38·5°C, 209 FN episodes were diagnosed (2·03/year), including 50 (24%) with SRE (0·49/year). The mixed Poisson regression rate ratio of FN with SRE in 39·0°C versus 38·5°C was 0·56 (95% upper confidence bound, 0·72; predefined non-inferiority margin for safety, 1·33). The corresponding rate ratio of FN was 0·83 (95% upper confidence bound, 0·98; predefined superiority margin for efficacy, 1·00).

Interpretation. In neutropenic children with chemotherapy for cancer, 39·0°C ear temperature was safe and efficacious. For Switzerland and comparable settings, 39·0°C can be recommended as new evidence-based standard fever limit except for patients with acute myeloid leukaemia or haematopoietic stem cell transplantation.

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INTRODUCTION

Fever in neutropenia (FN) is the most frequent potentially lethal complication of chemotherapy in children and adolescents with cancer. Emergency treatment including hospitalization and empirical start of broad-spectrum intravenous antibiotics[1–3] has decreased mortality to below 1% in paediatric FN.[4,5] Microbiologically defined infections are detected in only a minority of FN episodes.[2] Most patients with FN are thus overtreated, implying unnecessary hospitalization and further inconveniences for the patient, increased costs and the risk of antibiotic resistance.[6] Since risk-adapted treatment can reduce such overtreatment, a range of different clinical decision rules defining low-risk FN were developed in paediatric oncology.[7,8] Their clinical application, supported by recent guidelines, is increasing, though still not standard in most paediatric oncology centres.[3,9]

Despite the high personal and economic impact of FN diagnosis, there is a vast heterogeneity in the temperature limit used clinically for the definition of fever and thus FN.[10] This reflects the scarce evidence for rationally choosing such a fever limit.[3,11] Constraining FN diagnosis by using higher fever limits has a large potential to reduce overtreatment by avoiding hospitalization and antibiotics in patients with spontaneous defervescence.[10,12] Nevertheless, this may increase adverse events by delaying FN diagnosis and thus starting empirical antibiotics.[13]

This prospective trial primarily aimed to determine if a fever limit of 39·0°C is non-inferior to 38·5°C regarding safety in children and adolescents with cancer treated with chemotherapy.

Research in context

Evidence before this study

A multi-modal search was performed on February 10, 2020, aiming to find published results of past or current research on the optimal fever limit for FN, on the effect of changing this fever limit, and on related topics. We searched PubMed and clinicaltrials.gov using search terms for “fever or temperature”, “neutropenia or cancer” and “limit or definition”. We found no additional study in adult and paediatric FN, besides two studies conducted by the corresponding author himself. A retrospective two-center cohort study showed higher efficacy, i.e., a reduced number of FN diagnoses, and no increased rate of FN with bacteraemia for a higher fever limit. The second study prospectively assessed the efficacy but not the safety of a higher fever limit. This single-center observational study showed higher efficacy of a fever limit of 39·0°C when compared to lower temperatures. Despite the important implications on the diagnosis of FN the definition for fever varies between different pediatric oncology institutions and in a recent consensus paper on FN, no consensus for the fever limit could be reached among an international expert panel. In sum, before this trial there was no evidence and consensus on the optimal choice of a fever limit weighing efficacy against safety.

Added value of this study

This is the first prospective randomised, controlled, multicentre trial assessing safety and efficacy of a high versus low fever limit for FN definition. In neutropenic children and adolescents with chemotherapy for cancer an ear temperature of 39·0°C versus 38·5°C was found to be both non-inferior regarding safety and superior regarding efficacy.

Implication of all the available evidence

The results of this trial have substantial implications for the management of individual patients and for health economics. For Switzerland and countries with comparable settings, 39·0°C can now be recommended as evidence-based standard fever limit in

paediatric oncology except for patients with acute myeloid leukaemia or haematopoietic stem cell transplantation (HSCT). The responsible physician may decide to diagnose and treat FN below this limit if clinically indicated. The implementation of this high fever limit has been shown to be possible, but not trivial. In non-comparable settings, confirmatory trials are needed before clinical use.

METHODS

Study design and participants

This randomised controlled non-blinded multicentre trial, the Swiss Paediatric Oncology Group (SPOG) 2015 FN Definition study, was a multiple crossover non-inferiority trial for safety. Patients treated with chemotherapy for a malignancy were consecutively screened in all the six participating SPOG centres in Switzerland. Patients with any malignancy, aged ≥12 months to <18 years and treated with myelosuppressive chemotherapy expected to last ≥2 months, or ≥1 cycle of myeloablative chemotherapy followed by autologous haematopoietic stem cell transplantation (HSCT), were eligible for recruitment. Patients after allogeneic HSCT were excluded.

Data were collected and managed using REDCap electronic data capture tools.[14]

Patients, if able to judge, and their legal guardians gave written informed consent (IC) prior to trial entry. The trial was conducted in accordance with the Declaration of Helsinki and the Swiss Law, which refers to the current Good Clinical Practice guidelines. The protocol had been registered at www.clinicaltrials.com (NCT02324231) and approved by local ethics committees before starting patient recruitment. The full protocol, including the statistical analysis plan, is available on https://www.spog.ch/wp-content/uploads/2020/03/SPOG_FN_Protocol1.1_20161123_PDF.pdf .

Randomisation and masking

Monthly computer-generated 1:1 randomisation assigned patients, clustered via trial centres, to a high (39·0°C ear temperature) or low (38·5°C) fever limit for definition of FN. Trial centres were informed on the monthly allocation to fever limits by e-mail plus surface mail. Patients and investigators were not masked to treatment assignment.

Procedures

Temperature was measured in the ear by infrared tympanic thermometry using a Braun ThermoScan® 7 device (IRT 6520; steps displayed, 0.1°C; accuracy, ±0.2°C; clinical repeatability ±0.14°C)[15] throughout the trial.

Temperature was measured by parents at home if fever was suspected, plus at least twice daily in inpatients. The responsible local paediatric haemato-oncologist was immediately informed for temperatures ≥38·5°C or reduced general performance in both in- and outpatients. For outpatients with temperatures below the randomised limit or with known absence of neutropenia the responsible physician was free to decide how to proceed. Possible decisions were that the patient could safely remain at home or that he was seen at the emergency department and then sent back home or hospitalized for observation. Without FN diagnosis antipyretic treatment was strongly discouraged by the protocol. If the last complete blood count (CBC) was >48 (>72 in unequivocal situations) hours old, or suspected not to reflect the current absolute neutrophil count (ANC), a new CBC was performed. Neutropenia was defined as an ANC <0·5 G/L, or <1·0 G/L and expected to decline to <0·5 G/L within 48 hours.[11,16]

FN was diagnosed during neutropenia at ear temperatures reaching once the current limit, or below this limit with at least slightly elevated temperature (≥38·0°C; ≥37·5°C in patients repeatedly receiving antipyretics) if the responsible physician decided to do so. FN diagnosis implied emergency hospitalization, a minimal set of examinations, including blood culture (Supplementary Table S1), antipyretics when needed, and start

of empirical intravenous broad-spectrum antibiotics. Coverage of Gram-positive cocci (except methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci) and Gram-negative bacteria was required, but a specific anti-anaerobic coverage was not. Each centre chose antibiotics according to local resistance patterns (Supplementary Table S2). The fever limit used for FN diagnosis was as well used for decisions on diagnostics and supportive care during hospitalization, plus discharge.

Outcomes

The length of antibacterial therapy for FN defined the length of FN episodes. Restarting antibiotics within 7 days and with persistent neutropenia was counted as the same FN episode, as long as intravenous chemotherapy had not been restarted. All outcomes were tracked within these 7 days period.

The primary safety outcome was the rate of FN with ≥1 safety relevant event (SRE) per year of chemotherapy. SREs were defined as bacteraemia and/or serious medical complications. Bacteraemia was defined by the detection of a recognized pathogen from one or more blood cultures according to current definitions.[11,17] A serious medical complication was defined as death due to any cause during FN, admission to an intensive care unit (ICU), high dependency unit or other critical care unit for organ support, or severe sepsis (including septic shock) according to established definitions.[18] All SREs reported were verified for consistency by the senior author (RAA).

Secondary safety-related outcomes were clinically and microbiologically defined infection, unexplained fever, SIRS/sepsis, and relapse of primary infection.[11] Microbiologically defined infections included positive bacterial or fungal culture from a normally sterile body fluid or compartment (except bacteraemia), and detection of a viral antigen or product of polymerase chain reaction by a validated microbiological method.

Serious adverse events (SAE) were reported as requested by Good Clinical Practice guidelines.

Efficacy as secondary aim was assessed by the rate of FN per chemotherapy year as main efficacy outcome, rates of FN diagnosed at or below fever limit, the lengths of hospital stay, ICU stay, intravenous and oral antibiotics, and the delay of chemotherapy due to FN. This efficacy definition reflects the fact that a higher fever limit can avoid FN diagnosis, and thus overtreatment, in patients who spontaneously defervesce without treatment.[12]

Statistical Analysis

The trial was designed to reach a power of 80% to detect non-inferiority of the primary outcome for 39·0°C versus 38·5°C (alpha, 0·05; assumed rate ratio, 1·05; predefined non-inferiority limit, 1·33[19]). The raw sample size, determined by a series of 1000-fold random simulations of existing data,[10,20,21] was 116 FN with SRE. Accounting for three equally spaced interim analyses (Power family, O'Brian-Fleming type boundaries for success and for futility, delta=0[22]) led to a final sample size of 132 FN with SRE.

At the first interim analysis after 33 FN with SRE, the boundary for proven non-inferiority was crossed (z-value, 6·246; boundary, 3·312). The Study Committee decided to continue the trial in order not to compromise the impact of the results because of small patient numbers. The trial was stopped after the boundary for proven non-inferiority was again crossed at the second interim analysis after 66 FN with SRE (z-value, 5·492, boundary, 2·342).

For all outcomes, descriptive statistics using standard methods were performed. Three-level mixed regression analysis, with random intercepts per patient nested within centre was used to account for multiple randomisation periods per patient. Specifically, mixed Poisson regression with chemotherapy years as rate multiplier was used for outcomes assessed during chemotherapy. Mixed logistic and linear regression were used for

outcomes assessed within FN episodes. Multivariate analysis adjusting for chemotherapy intensity,[20,23] time since diagnosis, bone marrow involvement, type of central venous access device, and past FN was additionally performed.

For the primary outcome and the main efficacy outcome, no significant carry-over effects were detected within 24 hours after switching from 39·0°C to 38·5°C. For these outcomes, estimates and one-sided 95% upper confidence bounds (UCB) were calculated.

All other tests were two-sided, p-values <0·05 were considered significant, and 95% confidence intervals (CI) were calculated. All analyses were performed using R 3.5.1.[24] Specifically, the function “glmmPQL” from the “nlme” package[25] was used for mixed Poisson and mixed logistic regression.

All patients were treated per-protocol, defined by timely information of all relevant departments on the currently active fever limit. FN diagnosis below the randomised limit was allowed for clinical reasons and did not lead to exclusion from the per-protocol dataset. Therefore, the planned additional analyses in the intention-to-treat dataset were not done. There was no imputation for missing data.

Role of the funding source

The funders of the study had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. All authors had full access to all the raw data and the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patients and Randomisation Periods

Six of nine SPOG centres participated in this trial from April 2016 to August 2018. One centre used 39·0°C as standard fever limit outside the trial, while the others used lower limits, usually 38·5°C. Antibiotic prophylaxis for high risk patients was established in only one of these centres (Supplementary Table S2). Patients treated with chemotherapy for a malignancy were consecutively screened for eligibility in all centres. Four of 445 patients reported were not eligible for screening and 72 did not fulfill further eligibility criteria. Of the remaining 369 patients eligible for IC, 100 (27%) were not asked for or refused IC (Figure 1). Thus, a total of 269 patients were studied here. Their median age at screening was 8 years (interquartile range (IQR), 4 to 13), and 105 (39%) were female. Characteristics did not differ between patients eligible for screening and for IC, patients without IC on file and patients studied, except for recruitment differences between centres (Table 1).

The 269 patients were repeatedly randomised, with 1210 (48%) of 2547 randomisation periods and 92 (47%) of 195 chemotherapy years randomised to 39·0°C. All centres and 250 (93%) patients were randomised at least once to each limit. Patient characteristics, again except for centre, and FN risk factors were comparable between the two limits (Table 2).

FN Episodes

In total 360 FN episodes were reported (rate, 1·85 episodes per chemotherapy year; 95% CI, 1·66 to 2·05). Of the 269 patients, 158 (59%) had at least one FN episode (median per patient, 1; IQR, 0 to 2; maximum, 6). Of these 360 episodes, 279 (77%) were diagnosed at the randomised fever limit and 81 (23%) below this limit.

In 92 years randomised to 39·0°C, 151 FN episodes were diagnosed, whereof 53 (35%) were diagnosed below 39·0°C, including 22 (15%) below 38·5°C. Median temperature

at diagnosis was 39·0°C (IQR, 38·6°C to 39·2°C). In 103 years randomised to 38·5°C, 209 FN episodes were diagnosed, including 28 (13%) below 38·5°C. Median temperature at diagnosis was 38·7°C (IQR, 38·5 to 39·1; see Supplementary Figure S1).

Safety

At least one SRE was reported in 72 (20%) FN episodes (rate, 0·37 per chemotherapy year; 95% CI, 0·29 to 0·46). These were serious medical complications in 30 episodes (death, 0; ICU admission for organ support, 16; severe sepsis, 22) and bacteraemia in 56. In 92 years randomised to 39·0°C, a SRE was reported in 22 (15%) of 151 FN episodes, 9 (41%) of these 22 episodes were diagnosed below 39.0°C. In 103 years randomised to 38·5°C, a SRE was reported in 50 (24%) of 209 FN episodes, 6 (12%) of these episodes were diagnosed below 38.5°C (Table 3). The mixed Poisson regression rate ratio of FN with SRE for 39·0°C versus 38·5°C was 0·56, with a 95% UCB of 0·72 (predefined non-inferiority margin, 1·33). This was confirmed in multivariate analysis, accounting for 5 known risk factors (rate ratio, 0·53; 95% UCB, 0·67). The rate ratios of all components of SRE were consistently around 0·5 (Table 3). The non-significant difference in ICU treatment days was mainly due to two patients with ICU stays of 60 and 47 days, respectively, during 38.5°C.

Details on secondary safety outcomes are reported in Table 3. Within FN episodes diagnosed, safety outcomes were comparable between 39·0°C and 38·5°C (Supplementary Table S3).

In periods randomised to 39·0°C, 34 (35%) of the 98 FN diagnoses made at this limit were delayed by >1 hour compared to virtually applying 38·5°C, while this delay was ≤1 hour in 63 (64%; missing information in 1 episode). SRE were not more frequent in episodes with versus without delay (4 of 34, 12%; versus 9 of 63, 14%).

Nine serious adverse events were reported according to legal requirements. In all of them a potential relationship with the trial intervention could be excluded, see Supplementary Table S4 for details.

Efficacy

The mixed Poisson regression rate ratio of FN for 39.0°C versus 38.5°C, the main efficacy outcome, was 0·83, with a 95% UCB of 0·98 (predefined non-inferiority margin, 1·00). This was not fully confirmed in multivariate analysis (rate ratio, 0·85; 95% UCB, 1·03). The difference was due to significantly less FN diagnosed during the 39.0°C fever limit, despite significantly more FN diagnosed below this limit (Table 4). Correspondingly, hospitalization days per chemotherapy year were significantly lower for 39·0°C versus 38·5°C (Table 4). Within FN episodes diagnosed, efficacy outcomes were comparable between 39·0°C and 38·5°C (Supplementary Table S5). In periods randomised to 39·0°C, 13 (9%) FN episodes were avoided that would have been diagnosed applying 38·5°C.

Exploratory Analyses

Two unexpected findings led to exploratory analyses not defined in the trial protocol. First, the rate ratio of the primary outcome, FN with SRE in 39·0°C versus 38·5°C, expected to be slightly above one, was clearly lower. Exploratory analyses for heterogeneity between trial centres, timing of FN diagnosis, biased potential risk factors, side effects of medication, nosocomial infections, decreased staff awareness and further factors were all negative (Supplementary Table S6).

Second, the proportion of FN episodes diagnosed below the fever limit of 39·0°C was higher than expected, and non-specified “other reasons” were indicated more frequently than “reduced general condition” (48 of 151, 32% versus 24 of 151, 16%). Here, heterogeneity between trial centres was relevant (range, 13% to 82%) and associated with centre size. Specifically, this proportion exceeded 40% in the three centres

recruiting least patients. They had recruited 25% (66 of 269) patients and reported 57% (30 of 53) of these episodes. In two further centres using 38·5°C as standard limit outside the trial, FN diagnosis below the 39·0°C limit decreased during the course of the trial (Supplementary Figure S2).

DISCUSSION

This is the first prospective randomised, controlled, multicentre trial on the safety and efficacy of a high versus low fever limit for FN definition. In neutropenic children and adolescents with chemotherapy for cancer an ear temperature of 39·0°C versus 38·5°C was found to be both non-inferior regarding safety and superior regarding efficacy. Patients represented an unbiased sample of Swiss paediatric oncology patients regarding age, sex and type of malignancy. These results have substantial implications for the management of individual patients and for health economics.

In the setting of this trial, relevant difficulties to implement the fever limit of 39·0°C emerged in some centres. Reluctance of the responsible physicians to apply a higher than the accustomed fever limit is the most likely explanation. Implementation has been shown to be possible, however, in two centres using 38·5°C as standard limit outside the trial. These observations reflect the reality of implementing changes of clinical practice and increase the external validity of this trial.

During observation periods randomised to 39·0°C versus 38·5°C, the rate of FN episodes was lower, as expected, but the proportion of FN episodes with safety outcomes was not higher. This resulted in unexpected lower rates of FN with safety outcomes for 39·0°C. Exploratory analyses could not confirm any of the hypothesized mechanisms (Supplementary Table S6), though these analyses may have been underpowered. Our data do not allow to verify the controversially discussed hypothesis that early suppression of fever promotes infection.[26–29]

Regarding efficacy, 39·0°C versus 38·5°C reduced FN diagnosis by 17%, and FN hospitalization by 6 days per chemotherapy year. This would correspond to annual savings of around 1200 hospitalization days and costs of 2·4 million Swiss francs (2·4 million USD; 2000 USD per hospitalization day) for the 7·8 million inhabitants of Switzerland.[30]

A previous prospective single-centre study in Switzerland (n= 43) had found a 17% reduction in FN diagnosis applying 39·0°C versus 38·5°C as fever limits in paediatric patients.[12] We are not aware of other prospective studies assessing safety or efficacy of various temperature limits for FN definition in adult or paediatric oncology.

The main strengths of this trial were its repeated cross-over design which decreased sample size, and analysis of outcomes relative to chemotherapy duration. Including FN diagnoses below the randomised limit reflects clinical practice, and avoids potential underreporting and thus falsely declaring 39·0°C as safe. Further strengths were uniform temperature measurement devices, outcome tracking extended beyond stopping antibiotics, and verification of the primary outcome by an experienced paediatric oncologist.

The main limitation of this trial are the limited numbers of patients treated with intensive chemotherapy, like acute myeloid leukaemia-type and myeloablative regimens. Thus, results may not be valid in these patient groups. Thanks to the non-biased patient recruitment, however, these results seem to be valid for larger groups of patients with high-risk malignancies, like high risk ALL, though formal non-prespecified subanalyses were not performed. The trial was conducted in Switzerland, an industrialized country with mandatory health insurance and a high density of nine specialized tertiary care paediatric oncology centres for a population of 7·8 million inhabitants and around 200 new diagnoses per year.[30] Our results may not be valid in differing settings. Finally, the primary outcome was a clinically chosen composite of a wide range of adverse events, from bacteremia over ICU and severe sepsis to death. Choosing death, or alternatively ICU treatment as primary outcome would have led to a massively larger and longer study in this setting. However, the fact that the respective rate ratios for ICU admission, severe sepsis and bacteremia, as displayed in Table 3, gave very consistent results, increases the robustness of the findings.In conclusion, the use of a fever limit of 39·0°C

versus 38·5°C ear temperature is both safe and efficacious in neutropenic paediatric patients with chemotherapy for cancer. Choosing a higher fever limit for paediatric FN can reduce overtreatment by reducing over-diagnosis. For Switzerland and countries with comparable settings, 39·0°C can be recommended as evidence-based standard fever limit in paediatric oncology, with the exception of patients with acute myeloid leukaemia or HSCT. The responsible physician may decide to diagnose and treat FN below this limit if clinically indicated. The implementation of this high fever limit has been shown to be possible, but not trivial. In non-comparable settings, confirmatory trials are needed before clinical use.

AUTHORS' CONTRIBUTIONS

Conceived and designed the trial: NB, PKAA, FN, CA, MA, NK, KL, DN, KS, AS, OT, NXW, KZ, RAA.

Analyzed the data: RAA, CK

Wrote the paper: CK, NB, RAA

Recruited patients for trial participation: NB, FN, CA, MA, BE, KL, JR, KS, NXW, RAA

Approved the final version of this manuscript: CK, NB, PKAA, FN, CA, MA, BE, NK, KL, DN, JR, KS, AS, OT, NXW, MZ, KZ, RAA

DECLARATION OF INTEREST

Dr. Roessler reports personal fees from SOBI, personal fees from Roche, personal fees from Pierre Fabre, all for Advisory Board membership, and all outside the submitted work. All other authors declare no competing interests.

DATA SHARING

The study protocol, including the statistical analysis plan, is available within the article. Individual (de-identified) participant data will be available for qualified researchers who wish to access the data beginning three months following article publication; no end data. Proposals should be directed to roland.ammann@insel.ch; to gain access, data requestors will need to sign a data access agreement.

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FIGURE LEGENDS

Figure 1. CONSORT 2010 flow diagram. Refers to patients (n) and randomisation periods (RP) of patients.

TABLE LEGENDS

Table 1. Patient characteristics.

Table 2. Patient characteristics and risk factors for fever in neutropenia in randomisation periods.

Table 3. Safety related outcomes, analysis of fever limit 39·0°C versus 38·5°C per chemotherapy year.

Table 4. Efficacy related outcomes, analysis of fever limit 39·0°C versus 38·5°C per chemotherapy year.

SUPPLEMENTARY

Supplementary Figure S1. Highest ear temperatures before FN diagnosis.

Supplementary Figure S2. Highest ear temperatures before FN diagnosis during fever limit 39·0°C in centres 3 and 6 over course of trial.

Supplementary Table S1. Emergency examinations at diagnosis of fever in neutropenia.

Supplementary Table S2. Empirical intravenous antibiotics, antibacterial prophylaxis, and risk-stratification approach, by centre.

Supplementary Table S3. Safety related outcomes, analysis of fever limit 39·0°C versus 38·5°C per FN episode.

Supplementary Table S4. List of all serious adverse events (SAE).

Supplementary Table S5. Efficacy related outcomes, analysis of fever limit 39·0°C versus 38·5°C per FN episode.

Supplementary Table S6. Exploratory analyses on lower than expected rate ratio of the primary outcome.

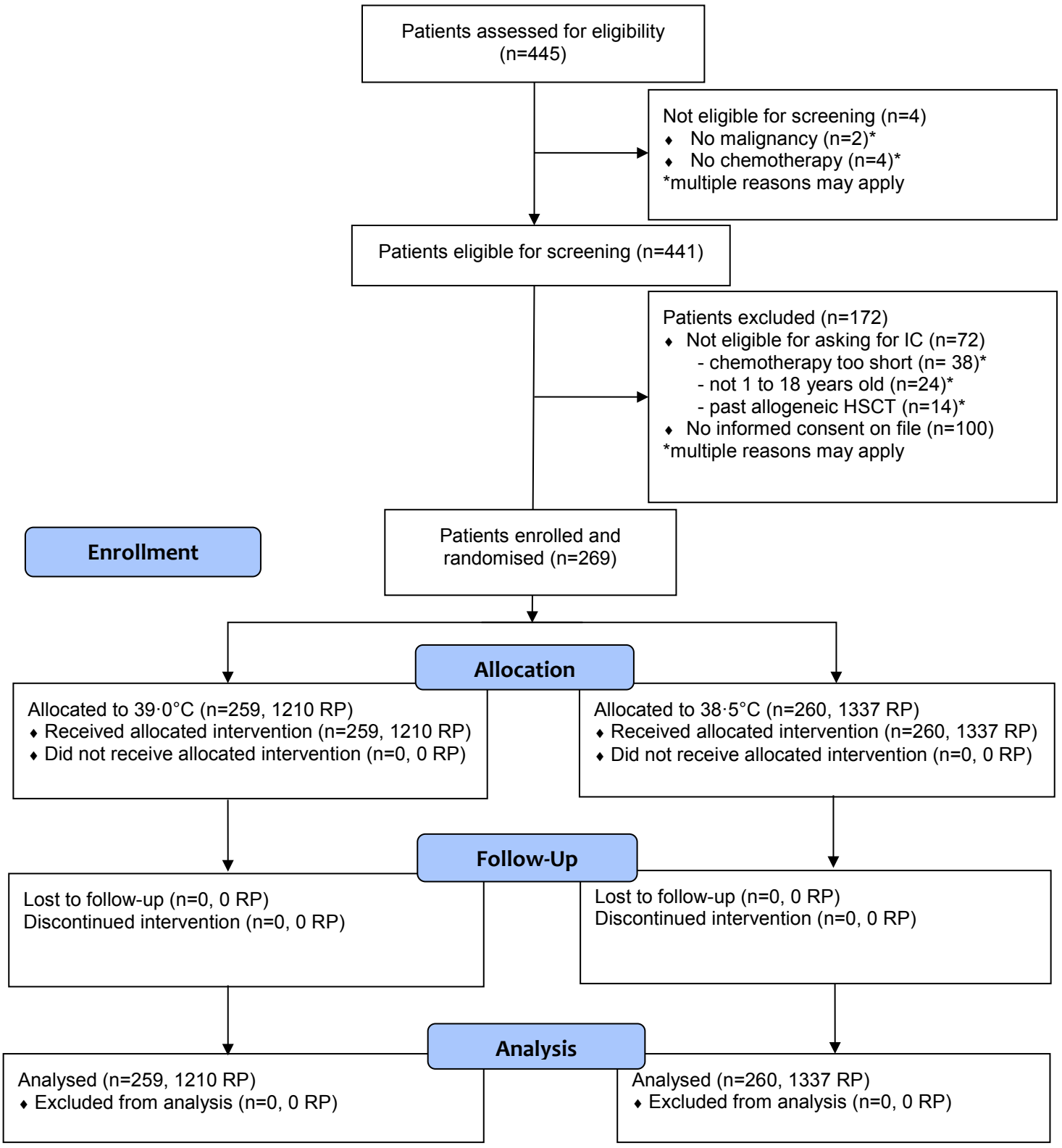

Figure 1: CONSORT 2010 flow diagram. Refers to patients (n) and randomisation periods (RP) of patients. HSCT denotes haematopoietic stem cell transplantation and IC informed consent.