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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Koenig C, Bodmer N, Agyeman PKA, et al. 39·0°C versus 38·5°C ear temperature as fever limit in children with neutropenia undergoing chemotherapy for cancer: a multicentre, cluster-randomised, multiple-crossover, non-inferiority trial. *Lancet Child Adolesc Health* 2020; published online June 1. https://doi.org/10.1016/S2352-4642(20)30092-4.

Supplementary Appendix – 39·0°C versus 38·5°C ear temperature as fever limit in neutropenic children undergoing chemotherapy for cancer: a multicentre, cluster-randomised, multiple-crossover, non-inferiority trial

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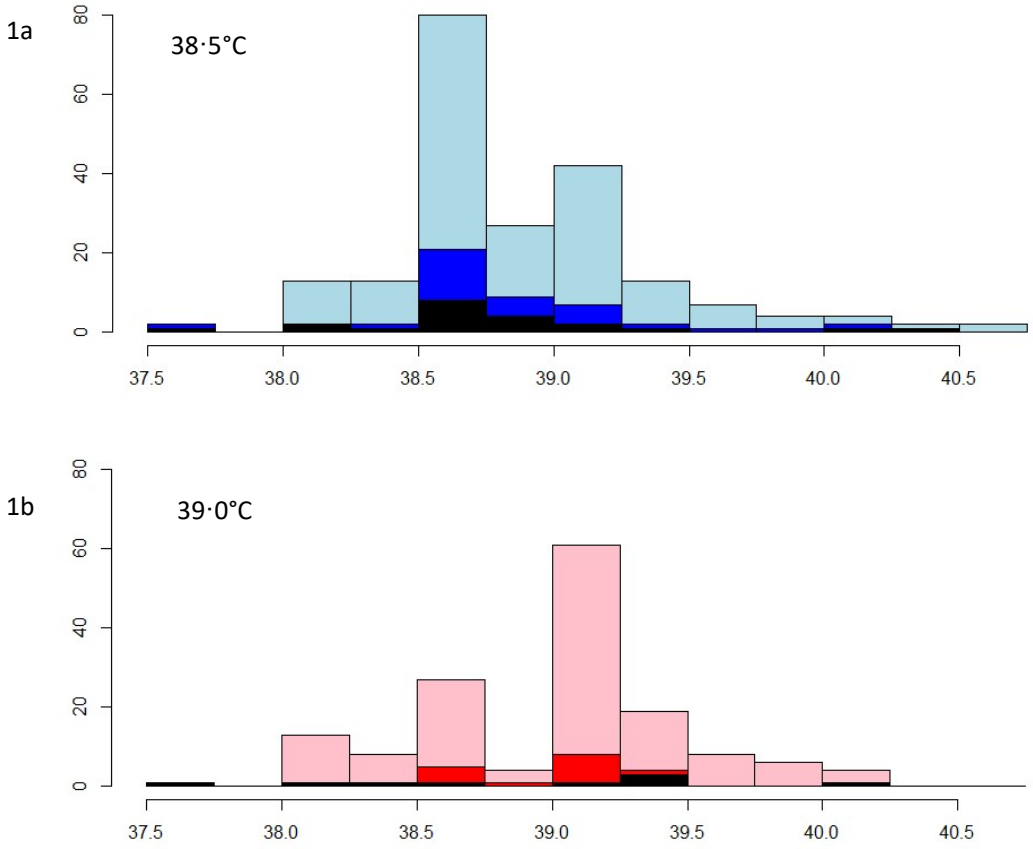
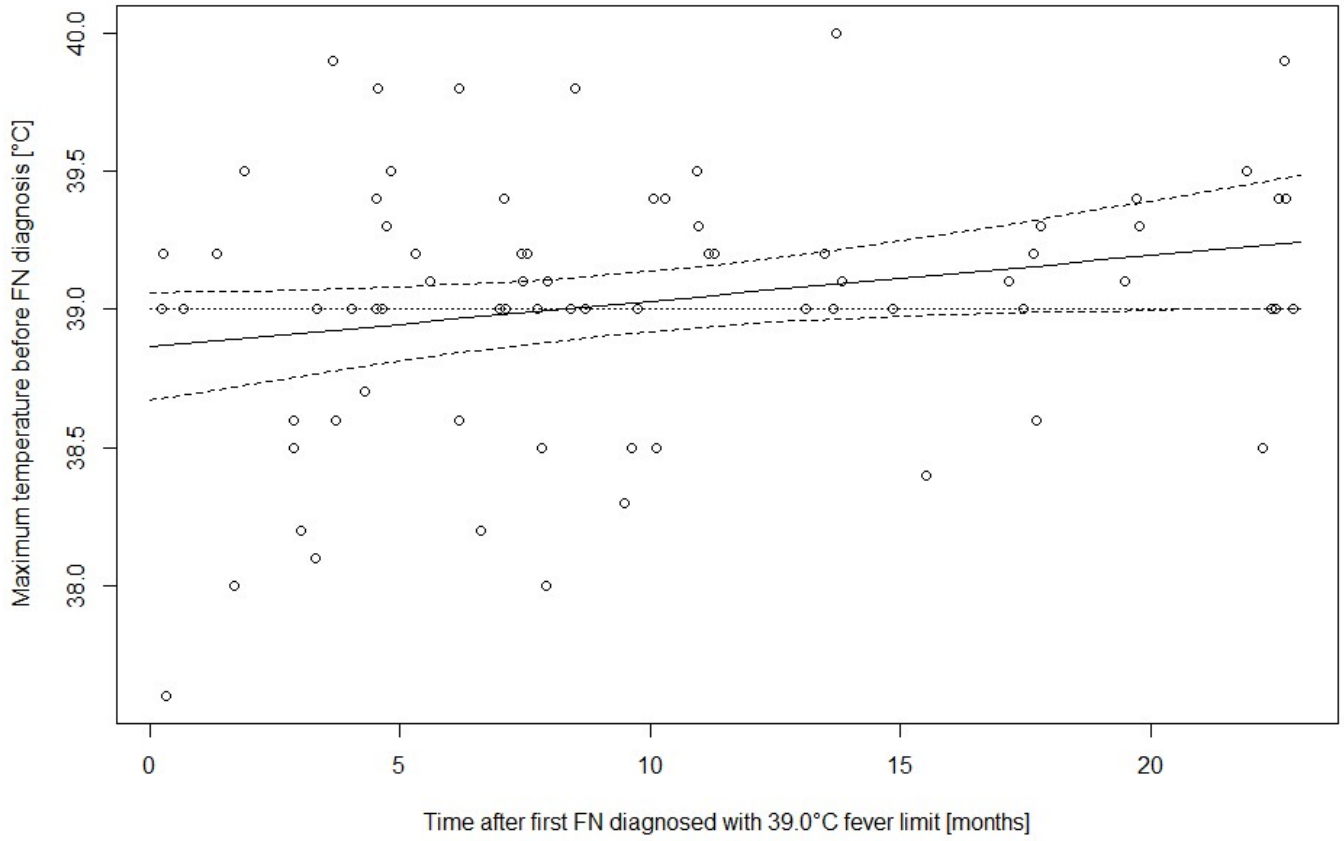
Supplementary Figures

Supplementary Figure S1. Highest ear temperatures before FN diagnosis.



Displayed are numbers of FN episodes by maximum temperature before FN diagnosis. 1a. Randomised fever limit 38·5°C ear temperature; color code: light blue: FN episodes without safety relevant event, dark blue: FN episodes with bacteraemia, black: FN episodes with serious medical complication. 1b. Randomised fever limit 39·0°C ear temperature; color code: light red: FN episodes without safety relevant event, dark red: FN episodes with bacteraemia, black: FN episodes with serious medical complication.

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 Tables

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

Minimum set of observations as defined in the trial protocol:

- History
- Physical examination
- Blood culture from CVAD analyzed in automated system or venipuncture in patients without CVAD
- CBC (if older than 12 hours)
- International normalized ratio of coagulation, serum creatinine, total bilirubin, alanine transaminase and C-reactive protein

CBC=complete blood count. CVAD=central venous access device.

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

Centre	Initial antibiotics	Routine systemic antibacterial prophylaxis beyond *Pneumocystis jirovecii* pneumonia prophylaxis	Risk-stratification approach
1	Ceftazidim/amikacin	No prophylaxis	None
2	Ceftriaxone/amikacin	No prophylaxis	Intensified antibiotics for septic patients, early discharge for low-risk patients
3	Piperacillin/tazobactam	Ciprofloxacin: AML, high risk/relapsed ALL	Intensified antibiotics for septic patients, early discharge for low-risk patients
4	Piperacillin/tazobactam	No prophylaxis	Intensified antibiotics for septic patients, early discharge for low-risk patients
5	Ceftriaxone/amikacin	No prophylaxis	Intensified antibiotics for septic patients, early discharge for low-risk patients
6	Meropenem	No prophylaxis	Intensified antibiotics for septic patients

ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia.

Supplementary Table S3. Patient characteristics.

	Consecutive patients eligible for screening	Patients eligible to be asked for IC	Patients with no IC on file†	Patients enrolled into the trial
Number of patients	441 (100%)	369 (100%)	100 (100%)	269 (100%)
Age at screening, median (IQR)	7 (4,13)	7 (4,13)	7 (4,13)	8 (4,13)
Female sex	179 (41%)	151 (41%)	46 (46%)	105 (39%)
Type of malignancy				
Acute lymphoblastic leukaemia	170 (39%)	157 (43%)	42 (42%)	115 (43%)
Acute myeloid leukaemia	15 (3%)	13 (4%)	6 (6%)	7 (3%)
Hodgkin lymphoma	30 (7%)	25 (7%)	5 (5%)	20 (7%)
Non-Hodgkin lymphoma	35 (8%)	29 (8%)	9 (9%)	20 (7%)
Central nervous system tumour	58 (13%)	47 (13%)	16 (16%)	31 (12%)
Other solid tumours	133 (30%)	98 (27%)	22 (22%)	76 (28%)
Centre*				
1	56 (13%)	46 (12%)	26 (26%)	20 (7%)
2	95 (22%)	87 (24%)	9 (9%)	78 (29%)
3	34 (8%)	34 (9%)	3 (3%)	31 (12%)
4	114 (26%)	93 (25%)	58 (58%)	35 (13%)
5	20 (5%)	15 (4%)	0 (0%)	15 (6%)
6	122 (28%)	94 (25%)	4 (4%)	90 (33%)

Data are presented as number (%) unless otherwise stated. IQR=interquartile range. *There were no significant differences between the groups except for centre ($p < 0{\cdot}001$). Percentages may not total 100 because of rounding. IC=informed consent. †not distinguishable whether patients were asked for informed consent or not.

Supplementary Table S4. Safety related outcomes, analysis of fever limit 39·0°C versus 38·5°C per FN episode.

	Total FN episodes	39·0°C	38·5°C	Mixed logistic regression, univariate		Mixed logistic regression, multivariate*	
Safety outcomes	**360 FN (100%)†**	**151 FN (100%)†**	**209 FN (100%)†**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Safety relevant event	72 (20%)	22 (15%)	50 (24%)	0·67 (0·40 to 1·14)	0·14	0·73 (0·42 to 1·25)	0·25
- Serious medical complication	30 (8%)	9 (6%)	21 (10%)	0·73 (0·40 to 1·32)	0·30	0·73 (0·39 to 1·35)	0·31
- Death	0	0	0	Model failure	··	Model failure	··
- ICU admission	16 (4%)	4 (3%)	12 (6%)	0·65 (0·36 to 1·19)	0·16	0·71 (0·34 to 1·48)	0·36
- Severe sepsis	22 (6%)	7 (5%)	15 (7%)	0·90 (0·50 to 1·65)	0.74	Model failure	··
- Bacteraemia	56 (16%)	18 (12%)	38 (18%)	0·78 (0·45 to 1·34)	0·37	1·05 (0·59 to 1·86)	0·87
Clinically defined Infections	92 (26%)	43 (28%)	49 (23%)	1·36 (0·84 to 2·20)	0·21	1·35 (0·83 to 2·21)	0·23
MDI (other than bacteraemia)	146 (41%)	53 (35%)	93 (44%)	0·76 (0·48 to 1·19)	0·23	0·72 (0·45 to 1·14)	0·17
SIRS/Sepsis	289 (80%)	126 (83%)	163 (78%)	2·61 (1·49 to 4·56)	0·0009	2·69 (1·52 to 4·77)	0·0009
Septic Shock (included in severe sepsis)	2 (1%)	0	2 (1%)	Model failure	··	Model failure	··
Relapse of infection	5 (1%)	2 (1%)	3 (1%)	Model failure	··	Model failure	··
Unexplained fever	160 (44%)	72 (48%)	88 (42%)	1·15 (0·74 to 1·80)	0·53	1·19 (0·75 to 1·88)	0·46

CI=confidence interval. FN=fever in neutropenia. ICU=intensive care unit. MDI=Microbiologically documented infection. SIRS=systemic inflammatory response syndrome.
* Adjusted for chemotherapy intensity, time since diagnosis, bone marrow involvement, type of central venous access device, and past FN; † Multiple outcomes per FN episode may apply.

Supplementary Table S5. List of all serious adverse events (SAE).

SAE Number	Serious adverse event	Relation with intervention studied*	Status	Death
2016.01	Septic shock, ICU	Relation excluded, reason 2	fully recovered	no
2016.02	Septic shock, ICU	Relation excluded, reasons 2,4	fully recovered	no
2016.03	Septic shock, ICU	Relation excluded, reason 3	fully recovered	no
2016.04	Septic shock, ICU, ARDS, ECMO, cerebral infarctions	Relation excluded, reason 2	stable deficiencies	no
2017.05	Septic shock, pneumonia, ICU	Relation excluded, reasons 1,2,4	fully recovered	no
2017.06	Confirmed disseminated *Aspergillus fumigatus* infection inclusive brain, ICU, decision palliation only, death	Relation excluded, reasons 1,2,4,5	death due to SAE†	yes†
2017.07	Septic shock, ICU	Relation excluded, reasons 2,5	fully recovered	no
2017.08	Septic shock, ICU, ECMO	Relation excluded, reasons 2,5	stable deficiencies	no
2018.09	ARDS, ICU	Relation excluded, reasons 1,2	fully recovered	no

ARDS=acute respiratory distress syndrome. ECMO=extracorporal membrane oxygenation. FN=fever in neutropenia. ICU=intensive care unit.
*Exclusion of a relation with the intervention studied (39·0° versus 38·5°C) was possible because of five reasons:
1. Patients with 39·0°C standard fever limit outside trial (patients in centre 2, except patients with acute myeloid leukaemia);
2. 38·5°C fever limit currently active at FN diagnosis (no delay of FN diagnosis by 39·0°C fever limit possible);
3. First temperature measured ≥38·5°C was ≥39·0°C (no delay of FN diagnosis by 39·0°C fever limit possible);
4. Maximum temperature before FN diagnosis <38·5°C (no delay of FN diagnosis by 39·0°C fever limit possible);
5. Other reasons specified by the trial centre investigator and confirmed by the trial chair.
†This patient died beyond the end of the FN episode, i.e., >7 days after stopping antibiotics.

Supplementary Table S6. Efficacy related outcomes, analysis of fever limit 39·0°C versus 38·5°C per FN episode.

	All FN episodes	39·0°C		38·5°C		Mixed linear regression, univariate	
Treatment days	**median**	**median**	**IQR, maximum**	**median**	**IQR, maximum**	**Coefficient (95% CI)**	**p-value**
- Hospitalization	6	5	4·0 to 9·5, 34	6	4·0 to 11·0, 78	-1·55 (-3·30 to 0·18)	0·081
- ICU treatment	0	0	0 to 0, 6	0	0 to 0, 60	-0·82 (-1·72 to 0·08)	0·076
- Intravenous antibiotics	5	5	4 to 9, 32	5	4 to 10, 61	-0·46 (-1·70 to 0·78)	0·47
- Oral antibiotics	0	0	0 to 0, 18	0	0 to 0, 13	0·45 (-0·07 to 0·97)	0·089
- Antiviral therapy	0	0	0 to 0, 16	0	0 to 0, 15	-0·09 (-2·15 to 0·30)	0·66
- Antifungal therapy	0	0	0 to 0, 34	0	0 to 0, 27	0·21 (-0·47 to 1·04)	0·62
Delay of chemotherapy	0	0	0 to 4·0, 35	0	0 to 6·75, 46	-1·00 (-2·23 to 0·24)	0·13

CI=confidence interval. FN=fever in neutropenia. ICU=intensive care unit. IQR=inter quartile range.

Supplementary Table S7. Exploratory analyses on lower than expected rate ratio of the primary outcome.

	Mechanism/Hypothesis	Analysis performed	Results	Interpretation
I Chance				
I.1 By chance	Chance	Three-level mixed regression analysis, with random intercepts per patient nested within trial sites, accounting for multiple randomization periods per patient	Rate Ratio 0·56, one-sided 95% UCB 0·72	negative
I.2 Poor fit of model	Poor fit of model, poor model	Model diagnostics by qq-plots: distribution of residuals/random effects.	Residuals: non-normal distribution, by definition (binary outcomes) Trial sites random effects: acceptable Patient random effects: acceptable	negative
II Unequal groups *(minimized by randomization)*				
II.1 Biased predefined risk factors	Risk factors not equally distributed between 38·5°C and 39·0°C.	Multivariate three-level mixed regression analysis with adjustment for chemotherapy intensity, time since diagnosis, bone marrow involvement, type of central venous access device, and past FN.	Confirmed univariate result: Rate Ratio 0·53, one-sided 95% UCB 0·67	negative
II.2 Heterogeneity between trial sites	Difference due to trial sites not to temperature limits.	Sensitivity analysis: one-by-one exclusion of sites	All 95% UCB below predefined non-inferiority margin of 1·33 Site 1 excluded: Rate Ratio 0·56, one-sided 95% UCB 0·73 Site 2 excluded: Rate Ratio 0·56, one-sided 95% UCB 1·10 Site 3 excluded: Rate Ratio 0·62, one-sided 95% UCB 0·80 Site 4 excluded: Rate Ratio 0·58, one-sided 95% UCB 0·76 Site 5 excluded: Rate Ratio 0·43, one-sided 95% UCB 0·58 Site 6 excluded: Rate Ratio 0·58, one-sided 95% UCB 0·76	negative
		Plotting site random effects	See results I.2	negative
		Meta-analysis-type of analysis of site specific results to assess variance explained by trial sites (Mantel-Haenszel method, DerSimonian-Laird estimator for tau[2])	No statistical signs of heterogeneity, $tau^2=0$, $I^2=0\%$, p=0·62	negative
II.3 Biased other risk factors	Other published potential risk factors not equally distributed between 38·5°C and 39·0°C	Data available: Binary characteristics: - Relapse - Severely reduced general condition - Haemoglobin (≥90g/l) - Leucocyte count (<0·3G/l) - ANC (<0·3G/l) - Platelet count (<50G/l)	- Relapse 38·5°C: 99/209 (4%); 39·0°C: 12/151 (8%); p-value†: 0·22 - Severely reduced general condition 38·5°C: 28/209 (13%); 39·0°C: 24/151 (16%); p-value†: 0·61 - Haemoglobin ≥90g/l: 38·5°C: 94/207(45%), 39·0°C: 50/151 (33%), p-value†: 0·025 (lower in 39·0°C) 38·5°C: median 85g/l; 39·0°C: median 81g/l; p-value‡: 0·066	negative negative negative

		Data available Continuous charactristics. - Haemoglobin - Leucocyte count - ANC - Platelet count No data available - C-reactive protein - Chills - Granulocyte-Colony Stimulating Factor - Antibiotic prophylaxis	- Leukocyte count <0·3G/l: 38·5°C: 74/209 (35%); 39·0°C: 50/151 (33%); p-value†: 0·73 38·5°C: median 0·51G/l; 39·0°C: median 0·50G/l; p-value‡: 0·72 - ANC <0·3G/l: 38·5°C: 84/130 (65%); 39·0°C: 76/89 (85%); p-value†: 0·0012 (lower in 39·0°C) 38·5°C: median 0·16G/l; 39·0°C: median 0·07G/l; p-value‡: 0·021 (lower in 39·0°C) - Platelet count <50G/l: 38·5°C: 107/208 (51%), 39·0°C: 83/150 (55%); p-value†: 0·53 38·5°C: median 48G/l; 39·0°C: median 46G/l; p-value‡: 0·93	negative negative negative
II.4 Seasonality	More SMCs in 38·5°C during winter due to seasonal viral/fungal infections.	Comparison of randomised months in winter (December to March) versus non-winter (April to November).	- Winter months (December to March) 38·5°C: 449/1337 (34%); 39·0°C: 367/1210 (30%); p-value†: 0·087	negative
II.5 Timing of FN diagnosis	FN decision during out-of-office time (night or at the weekend) more common in 38·5°C, via delays at home and in the ED (understaffing)	Comparison of time of fever measurements at FN diagnosis.	- Nighttime (20:00 to 07:59) 38·5°C: 83/209 (40%); 39·0°C: 68/151 (45%); p-value†: 0·37 - Weekend (Saturday, Sunday) 38·5°C: 55/209 (26%); 39·0°C: /151 (18%); p-value†· 0·079 - Combined (out-of-office time: nighttime or Saturday/Sunday) 38·5°C: 112/209 (54%); 39·0°C: 80/151 (53%); p-value†: 0·99	negative negative negative
III. Treatment related				
III.1 Fever suppression	Fever suppression also suppresses the beneficial effects of fever	Not possible to test. Literature search in PubMed 02/2019	Many studies were identified about the influence of antipyretics on outcomes in animals and humans.[1] A prospective, randomised study in critically ill patients had shown a higher mortality and increased SIRS score in critically ill patients with more aggressive treatment with antipyretics compare to a permissive group.[2] An observational study confirmed these results with the finding of an increased morality in sepsis patients who received antipyretics.[3] A later prospective, randomised study has not confirmed these results in critically ill patients,[4] nor did two retrospective studies in patients with sepsis/septic shock[5] or critically ill patients with neurotrauma or hypoxia.[6]	controversial
III.2 Side effects of medication	Leading to more SMC but not bacteraemia in 38·5°C	Checking numbers and comparison of bacteraemia versus SMC in 38·5°C	Bacteraemia in 38·5°C: 38/56 (0·68; 95% CI, 0·54 to 0·80) SMC in 38·5°C: 21/30 (0·70; 95% CI, 0·51 to 0·85) p-value§: 1.00	negative

III.3 Nosocomial infections	SRE due to nosocomial infections acquired at the hospital	Comparison of SRE occurring later during FN episode in 38·5°C versus 39·0°C.	Late SMC/any SMC: - Severe sepsis later than 6hours from diagnosis: 38·5°C: 1/8 (13%); 39·0°C: 1/4 (25%); p-value†: 0·85 - ICU admission: no information on time point - Deaths: no deaths	negative
		Comparison of bacteraemia detected only after start of antibiotics (late bacteraemia) in 38·5°C versus 39·0°C.	Late bacteraemia / any confirmed bacteraemia 38·5°C: 11/38 (0·29; 95%CI 0·16 to 0·46); 39·0°C: 4 /18 (0·22; 95%CI 0·07 to 0·48); p-value§: 0·84	negative
		Check whether there are typical bacteria for nosocomial infections in late bacteraemia	Bacteria detected in late bacteraemia 38·5°C: *Actinomyces odontolyticus*; *Micrococcus luteus*; *Klebsiella pneumoniae ESBL*; *Staphylococcus aureus* + *Staphylococcus coagneg*; *Staphylococcus coagneg* + *Staphylococcus coagneg*; *Bacillus cereus*; *Staphylococcus coagneg*; *Staphylococcus coagneg*; *Staphylococcus aureus*; *Enterococcus faecium* + *Staphylococcus epidermidis; Enterobacter cloacae complex* 39·0°C *Enterococcus faecalis* + *Stomatococcus mucilaginosus*; *Klebsiella pneumoniae*; *Micrococcus luteus*; *Enterococcus faecium*	negative
IV. Care related				
IV.1 Decreased staff awareness	Less caution of physicians and nurses during 38·5°C (falsely feel safe)	Comparison of bacteraemia and SMC occurring later during FN episode in 38·5°C versus 39·0°C.	See results III.2	negative
		Check distribution of highest temperature before FN diagnosis	Temperature at diagnosis ≥ 39·5°C 38·5°C: 19/209 (9%, 95% CI 6 to 14%); 39·0°C: 18/151 (12%, 95% CI 7 to 18%); p-value§: 0·49 See Supplementary Figure 1	negative
IV.2 Time to antibiotics	Timespan from fever to antibiotic administration (TTA) is longer in 38·5°C	Comparison of TTA between 38·5°C and 39·0°C	TTA from 38·5°C to start of antibiotics: 38·5°C: median 125min; 39·0°C: median 160min p-value‡: <0·0001 (shorter TTA in 38·5°C)	negative
			TTA from arrival at the trial site to start of antibiotics 38·5°C: median 82min; 39·0°C: median 110min p-value‡: 0·019 (shorter TTA in 38·5°)	negative

ANC=absolute neutrophile count. CI=confidence interval. coagneg=coagulase-negative. FN=fever in neutropenia. SMC=serious medical complication. SRE=safety relevant event. TTA=time to antibiotics. UCB=upper confidence bound.
† Pearson's Chi-squared test with Yates' continuity correction.
‡ Wilcoxon rank sum test with continuity correction.
§ 2-sample test for equality of proportions with continuity correction.

Supplementary References

1 Barone JE. Fever: Fact and fiction. *J Trauma* 2009; **67:** 406–9.

2 Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg Infect* (Larchmt) 2005; **6:** 369–75.

3 Lee BH, Inui D, Suh GY, et al. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. *Crit Care* 2012; **16:** R33.

4 Young P, Saxena M, Bellomo R, et al. Acetaminophen for fever in critically ill patients with suspected infection. N Eng J Med 2015;373:2215–24.

5 Mohr NM, Fuller BM, Skrupky LP, et al. Clinical and demographic factors associated with antipyretic use in gram-negative severe sepsis and septic shock. *Ann Pharmacother* 2011; **45:** 1207–16.

6 Gozzoli V, Schottker P, Suter PM, Ricou B. Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. *Arch Intern Med* 2001; **161:** 121–3.