SPOG 2015 FN Definition

A Swiss Paediatric Oncology Group (SPOG) initiated multi-center open-label randomized controlled multiple crossover non-inferiority trial on safety of a high versus low temperature limit defining fever in pediatric patients with cancer at risk for fever in chemotherapy-induced neutropenia (FN)

Study Committee

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SPOG 2015 FN Definition

A Swiss Paediatric Oncology Group (SPOG) initiated
multi-center open-label randomized controlled multiple crossover non-inferiority trial on safety of a high versus low temperature limit defining fever in pediatric patients with cancer at risk for fever in chemotherapy-induced neutropenia (FN)

Study Type:	Health related interventional clinical trial
Study Categorisation:	Risk category B according to ClinO art. 61
Study Registration:	www.clinicaltrials.gov: NCT02324231 www.kofam.ch: SNCTP000001776
Study Identifier:	SPOG 2015 FN Definition
Sponsor	Swiss Paediatric Oncology Group (SPOG)
Principal Investigator:	Roland A Ammann, MD; University of Bern; Department of Pediatrics; Inselspital; CH-3010 Bern; roland.ammann@insel.ch
Investigational Product:	None
Protocol Version / Date:	1.1 / November 23, 2016

Signatures:

The Sponsor and the Study Chair/Principal Investigator have approved this protocol version, and confirm hereby to conduct the study according to the protocol, the current version of the World Medical Association Declaration of Helsinki and all legally applicable laws and requirements.

Sponsor Representatives:

Prof Dr med Felix Niggli, SPOG President

Place/Date: Zürich, 24.11.2016 Signature: F. Niggli

Isabelle Lamontagne-Müller, SPOG Managing Director

Place/Date: Bern, 9.12.2016 Signature: I. Lamontagne-Müller

Study Chair and Principal Investigator:

Prof Dr med Roland A Ammann, Inselspital Bern

Place/Date: Zürich, 24-11-16 Signature:

Signature: Local Principal Investigators at each study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki and all legally applicable laws and requirements.

Site: Bern

Principal Investigator: Roland Ammann

Place/Date: Zürich, 24-11-16 Signature:

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STUDY SYNOPSIS

Sponsor	Swiss Paediatric Oncology Group (SPOG)
Study Title:	A Swiss Paediatric Oncology Group (SPOG) initiated multi-center open-label randomized controlled multiple crossover non-inferiority trial on safety of a high versus low temperature limit defining fever in pediatric patients with cancer at risk for fever in chemotherapy-induced neutropenia (FN)
Short Title / Study ID:	SPOG 2015 FN Definition
Protocol Version and Date:	Version 1.1, November 23, 2016
Trial registration:	www.clinicaltrials.gov: NCT02324231, registered Dec 23, 2014 www.kofam.ch: SNCTP000001776, registered Dec 18, 2014
Study category and Rationale	Clinical trial (randomly assigned intervention) without investigational medicinal product (IMP), without medical device (MD), risk category B (more than minimal risk) according to ClinO art. 61.
Clinical Phase:	Not applicable (no IMP, no MD)
Background and Rationale:	Fever in neutropenia (FN), if due to infection, is the most frequent potentially lethal complication of chemotherapy for cancer in children and adolescents. Emergency hospitalization and empirical treatment with i.v. broad-spectrum antibiotics have reduced lethality from >50% in certain high risk situations to <1%, at the price of high morbidity and use of resources. Despite the high economic and personal impact of FN diagnosis, there is a vast heterogeneity regarding the temperature limit defining fever (TLDF), used for FN. This reflects the scarce evidence for rationally choosing a TLDF. In a Swiss single-center study, a high versus low TLDF (39.0°C versus 38.5°C measured in the ear) had relevantly reduced the rate of FN diagnoses, and thus hospitalizations and intravenous antimicrobial therapies, by 21%. The study was too small to reliably assess safety. This study primarily aims to assess the safety of a high versus low TLDF.
Objective(s):	Primary objective: to determine if a high TLDF (39.0°C) is non-inferior to a low TLDF (38.5°C) regarding safety. Secondary objective: to determine if a high TLDF is superior to a low TLDF regarding efficacy. Tertiary objective: to use the data for development of risk prediction rules, and for external validation of published risk prediction rules.

Outcome(s):	Primary outcome: Poisson rate of clinically defined FN (FN_{Clin}) with ≥1 safety relevant event (SRE; composite outcome: bacteremia and/or serious medical complication) per chemotherapy exposure time (CET). Secondary safety-related outcomes: A. Times (hh:mm) of measurement of fever – telephone to study site – arrival at emergency department – prescription of antibiotics – start and end of first dose of i.v. antibiotics B. Adverse events: clinically / microbiologically documented infection, unexplained fever, sepsis / severe sepsis / septic shock, relapse of primary infection C. Only for currently active high TLDF: delay time between crossing low and high TLDF; delayed FN diagnosis by high vs. low TLDF Secondary efficacy-related outcomes: D. Poisson rate of FN_{Clin} per CET E. Poisson rate of FN_{TLDF} and FN_{Below} per CET (see 5.1.3) F. Duration (days) of hospitalization, intensive care unit (ICU) treatment, i.v. antibiotics, p.o. antibiotics, any antibiotics, delay of chemotherapy for FN G. Only for currently active high TLDF: simultaneous and avoided FN diagnosis (see 5.1.4) by applying high vs. low TLDF
Primary analysis	Mixed Poisson regression of the rate ratio of the primary outcome of high versus low TLDF, with chemotherapy exposure time as rate multiplier, and random intercepts per patient nested within study site, in the per protocol set. If the upper (one-sided) 95% confidence border of this rate ratio is below the non-inferiority margin, i.e., <1.33, non-inferiority of the high versus low TLDF regarding safety will be claimed.
Study design:	Open-label cluster-randomized controlled parallel-group multiple-crossover non-inferiority trial, with study sites as units of randomization, and patients as units of analysis.
Inclusion / Exclusion criteria:	Inclusion criteria - Chemotherapy treatment because of any malignancy expected to last ≥2 months at time of recruitment for myelosuppressive therapy, or at least 1 cycle of myeloablative chemotherapy followed by autologous hematopoietic stem cell transplantation - Age ≥12 months and <18 years at time of recruitment - Written informed consent from patients and/or parents Exclusion criteria - Infants <12 months (reason: difference in temperature measurement method) - Past allogeneic hematopoietic stem cell transplantation - Denied written informed consent from patients and/or parents Reason for inclusion of children/adolescents (vulnerable participants): important differences in core FN characteristics between children/adolescents and adults
Measurements and procedures:	Outcomes are determined using clinically available information (patient charts, results of laboratory tests performed for clinical reasons).

Intervention:	Randomization, repeated every month (implying potentially repeated cross-over) assigns patients, via study sites, for periods of 1 month each, to - high (39.0°C) TLDF arm, for definition of FN - low (38.5°C) TLDF arm, for definition of FN Temperatures are measured in the ear by infrared tympanic thermometry throughout the study. If clinically indicated, the responsible pediatric hemato-oncologist of the study site (local PHO) is allowed to make the diagnosis of FN at lower temperatures in both arms. Diagnosis of FN implies emergency hospitalization, essential laboratory tests and start of empirical intravenous broad-spectrum antimicrobial therapy. The responsible local PHO decides on the antimicrobial substance used (which is thus not an IMP here), and on all further diagnostic and therapeutic measures.
Number of Participants with Rationale:	Around 400 patients, the majority will be assigned at least once to each of both arms (multiple crossover). Sample size calculations and thus decisions when to perform interim and final analyses refer to FN_{Clin} episodes with SRE. Based on 1000-fold random simulation studies, 132 FN_{Clin} with SRE are needed to reach 80% power to detect non-inferiority of the rate ratio of FN_{Clin} with SRE of high versus low TLDF, assuming a rate ratio of 1.05, at alpha = 0.05 and with a non-inferiority limit of 1.33, after accounting for up to 3 interim analyses. These 132 FN_{Clin} with SRE correspond to 550 FN, to 372 years of cumulative chemotherapy exposure time, and to around 400 patients.
Study Duration:	3.7 years
Study Schedule:	First patient in (planned): March 2016 Last patient out (planned): October 2019
Investigator(s):	Chair of Study Committee, and Principal Investigator: Prof. Dr. med. Roland Ammann, Pediatric Hematology/Oncology, Department of Pediatrics, University of Bern, Inselspital, CH-3010 Bern, Switzerland. phone +41 31 632 21 11; fax +41 31 632 95 07; roland.ammann@insel.ch Vice-Chair of Study Committee: Dr. med. Nicole Bodmer, Pediatric Oncology, University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zürich, Switzerland. phone +41 44 266 71 11; fax +41 44 266 79 14; nicole.bodmer@kispi.uzh.ch See Appendix A for the list of Local Principal Investigators.
Study Sites:	Multi-center, all SPOG member institutions
Statistical Considerations:	Up to 3 interim plus 1 final analysis (Power family of one-sided group sequential tests, delta=0), adjustments for past analyses to maintain an overall alpha of 0.05.
Legal Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki and all national legal and regulatory requirements.

STUDY SUMMARY IN LOCAL LANGUAGE

SPOG 2015 FN Definition

Eine Studie der Schweizerischen Pädiatrischen Onkologie Gruppe (SPOG) über die Sicherheit einer hohen versus tiefen Fiebergrenze bei Kindern und Jugendlichen mit einer Krebserkrankung mit dem Risiko von Fieber während eines durch Chemotherapie verursachten Mangels an weissen Abwehr-Blutkörperchen (Neutropenie).

Die häufigste potentiell tödliche Nebenwirkung der Chemotherapie bei Krebserkrankungen ist Fieber in Neutropenie (FN), d.h. Fieber während eines vorübergehenden Mangels an weissen Abwehr-Blutkörperchen. Die Mehrheit der Kinder und Jugendlichen mit einer Krebserkrankung hat während der Chemotherapie mindestens einmal FN. Dank der Standardbehandlung mit Notfallhospitalisation und sofortigem Start von intravenösen Breitbandantibiotika sterben heute <1% der Kinder mit FN. Jedoch werden bakterielle Infektionen nur bei circa ¼ der FN nachgewiesen. Entsprechend werden circa ¾ aller FN übertherapiert, mit an sich unnötigen Hospitalisationen, Antibiotikatherapien, und hohen Kosten. Ein Ansatz zur Reduktion dieser Übertherapie ist, bei niedrigem Komplikationsrisiko die Diagnose FN gar nicht erst zu stellen, beispielsweise durch Erhöhung der Fiebergrenze zur Definition von FN. Diese Grenze wird aktuell in der Kinderonkologie sehr uneinheitlich gehandhabt und variiert zwischen 37.5°C und 39.0°C.

Es ist bekannt, dass eine höhere Fiebergrenze die Anzahl der FN Diagnosen reduziert. Es ist jedoch nicht bekannt, ob diese Grenze auch sicher ist, d.h., ob kein höheres Komplikationsrisiko wegen verspätetem Therapiebeginn besteht.

In dieser Studie wird deshalb untersucht, ob eine höhere Fiebergrenze (Ohrtemperatur 39.0°C) bezüglich Sicherheit nicht schlechter ist als eine tiefere Grenze (38.5°C). Die Studie ist eine sogenannte randomisierte kontrollierte Studie, bei der die für die Patienten gültige Fiebergrenze monatlich zufällig (randomisiert) gewechselt wird, um den Vergleich möglichst aussagekräftig zu machen. Die Studie wird an mehreren Zentren durchgeführt, die alle Mitglieder der Schweizerischen Pädiatrischen Onkologie Gruppe sind. Die vorgesehene Studiendauer beträgt rund 4 Jahre, und es werden circa 400 Kinder und Jugendliche mit Krebserkrankung an der Studie teilnehmen.

Falls die Sicherheit der höheren Fiebergrenze nachgewiesen wird, können Zentren mit aktuell tieferer Fiebergrenze auf diese höhere Fiebergrenze wechseln, was zu einer Reduktion der Übertherapie von FN führen wird. Falls die Sicherheit nicht nachgewiesen werden kann, sollten Zentren mit aktuell höherer Fiebergrenze auf die tiefere Fiebergrenze wechseln, was die Behandlungssicherheit erhöhen wird.

ABBREVIATIONS

AE	Adverse Event
AE	Absolute Neutrophil Count
AML	Acute Myeloid Leukemia
CBC	Complete Blood Count
CEC	Competent Ethics Committee
CET	Chemotherapy Exposure Time
CI	Confidence Interval
CRF	Case Report Form
CVAD	Central Venous Access Device
FN	Fever in Neutropenia
FN_{Below}	FN_{Clin} diagnosed below the currently active TLDF
FN_{Clin}	Clinically defined FN episode
FN_{TLDF}	FN_{Clin} diagnosed at/above the currently active TLDF
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ITT	Intention To Treat
MD	Medical Device
MDI	Microbiologically Documented Infection
PHO	Pediatric Hemato-Oncologist
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SMC	Serious Medical Complication
SOP	Standard Operating Procedure
SPOG	Swiss Pediatric Oncology Group
SRE	Safety Relevant Event
TLDF	Temperature Limit Defining Fever
UCB	Upper Confidence Bound

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

The Sponsor of this study is the Swiss Paediatric Oncology Group.

The central office of the Sponsor is located at:

- SPOG Office, Effingerstrasse 33, CH-3008 Bern, Switzerland
- E-mail: info@spog.ch
- Phone: +41 31 389 91 89
- Fax: +41 31 508 41 42

The SPOG Office is responsible for regulatory affairs and monitoring of the study for all participating study sites.

1.2 Study Chair

The Sponsor delegates certain responsibilities to the Study Chair who will perform the delegated Sponsor's tasks and responsibilities according to the Swiss Human Research Act of 30 September 2011 (HRA) in connection with the Swiss Ordinance about Clinical Trials in Human Research of 20 September 2013 (ClinO).

The Study Chair constitutes the study committee and is responsible for all its activities including development of the study protocol, CRF design, writing patient information and informed consent documents, interim analysis and interpretation of data and writing of the final study report. The members of the study committee will sign a confidentiality agreement regarding patient data (see 2.7) and other confidential aspects of the study.

1.3 Study Committee

See page 1 for the list of Study Committee members.
The Study Committee can be contacted via:
Study Chair: Prof Dr med Roland A Ammann; Pediatric Hematology/Oncology; Department of Pediatrics; University of Bern; Inselspital; CH-3010 Bern; Switzerland;
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Study Vice Chair: Dr med Nicole Bodmer; Pediatric Oncology, University Children's Hospital, Steinwiesstrasse 75; CH-8032 Zürich; Switzerland;
phone +41 44 266 71 11; fax +41 44 266 79 14; nicole.bodmer@kispi.uzh.ch

1.4 Study Statistician

The Study Chair, Prof Dr med R. Ammann, who holds a Diploma of Advanced Studies in Applied Statistics, performs as well the duties of the Study Statistician (see 1.2).

1.5 Study chair site, study center

The Study Chair site, in the following called the study center is responsible for the central data collection and management of all study data collected from all participating sites (see 12.1 and 12.2). The study center can be contacted via:

Study Chair: Prof Dr med Roland A Ammann; Pediatric Hematology/Oncology; Department of Pediatrics; University of Bern; Inselspital; CH-3010 Bern; Switzerland;
phone +41 31 632 21 11; fax +41 31 632 95 07; roland.ammann@insel.ch

1.6 Principal Investigators

See Appendix A.

2. ETHICAL AND REGULATORY ASPECTS

2.1 Study registration

The study is registered in www.clinicaltrials.gov (NCT02324231) and in the Swiss National Clinical Trial Portal (SNCTP, www.kofam.ch, SNCTP000001776).

2.2 Categorisation of study

Clinical trial (randomly assigned intervention) without investigational medicinal product (IMP), without medical device (MD)), risk category B (more than minimal risk) according to ClinO art. 61 [1,2].

2.3 Competent Ethics Committee (CEC)

The study protocol will be submitted to the lead CEC and all involved local CECs according to the swissethics concept for multicenter studies. The responsible investigator at each site ensures that approval from the CEC is available before starting with the enrollment of patients. No changes are made to the protocol without prior approval by Sponsor and CEC, except where necessary to eliminate apparent immediate hazards to study participants.
Premature study end or interruption of the whole study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.9.

2.4 Ethical conduct of the study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki [3] and the Swiss Law [1,2]. The CEC will receive annual safety reports and will be informed about study stop/end in agreement with legal requirements.

2.5 Declaration of interest

There is no conflict of interest for the Sponsor and for all members of the Study Committee.

2.6 Patient and parent/legal representative information, and informed consent

The investigators will explain to each patient and/or the parents/legal representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each patient and/or the parents/legal representative will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect the subsequent medical assistance and treatment. The patient and/or parents/legal representative are informed that the medical records may be examined by authorised individuals other than their treating physician. All patients and/or the parents/legal representative will be provided a patient information sheet and/or a parent information sheet and a consent form describing the study and providing sufficient information for the patient and/or the parents to make an informed decision about study participation. A sufficient time frame of at least two days will be given to make this decision.

The patient information sheet, the parent information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The formal consent of a patient and/or parents/legal representative, using the approved consent form, must be obtained before the patient is submitted to any study procedure.

If a minor and/or patient under tutelage is capable of judgment, his/her assent is collected (required from the age of 14 years) in addition to the consent of the parents/legal representative on the informed consent form. If a patient incapable of judgment displays signs and symptoms showing that he/she is unwilling to participate in the study, he/she is excluded from participation.

The patient and/or the parents/legal representative should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be

retained as part of the study records.

2.7 Patient privacy and confidentiality

The investigator affirms and upholds the principle of the patients' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the patients shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

For quality assurance or quality control purposes, authorised representatives of the sponsor, or the CEC may require direct access to study documentation and medical records relevant to the study, including patients' medical history.

2.8 Early termination of the study

Upon recommendation of the study committee the Sponsor may terminate the study prematurely in case of certain circumstances, e.g., ethical concerns, insufficient participant recruitment, when the safety of the participants is doubtful or at risk, respectively, alterations in accepted clinical practice that make the continuation of the study unwise, or early evidence of benefit or harm (see 11.3, 11.4.4).

2.9 Protocol amendments

The Study Committee may amend the protocol. Substantial amendments are only implemented after approval by the Sponsor and the CEC. All non-substantial amendments are communicated to the CEC within the Annual Safety Report.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the CEC. Such deviations shall be documented and reported to the Sponsor and the CEC as soon as possible.

3. BACKGROUND AND RATIONALE

3.1 Background and rationale

3.1.1 Fever in neutropenia in pediatric patients with cancer

Fever in neutropenia (FN), if due to infection, is the most frequent potentially lethal complication of chemotherapy in pediatric and adult patients with cancer. The specific rate of FN in pediatric oncology strongly depends on the myelosuppressive intensity of chemotherapy. This rate varies from <0.1 to 0.8 FN episodes per month of chemotherapy in Switzerland. At least one episode of FN is diagnosed in more than half of pediatric patients with chemotherapy [4]. Standard treatment of FN includes emergency hospitalization and the empirical (before detection of a bacterial infection) start of broad-spectrum i.v. antibiotics [5-7]. This has decreased lethality to below 1% in pediatric FN [8,9].

It is known, however, that a microbiologically documented infection (MDI), including bacteremia, is detected in only about a quarter of FN episodes, and any adverse event (AE) occurs in less than half of them [6]. The proportion of FN with MDI is increased to more than 50% if polymerase chain reaction-based methods for the detection of viral, bacterial and fungal infections are added to conventional diagnostics. The clinical implications of such results are not yet known, and these methods are not used routinely [7,10,11].

The majority of patients with FN is thus most likely overtreated, implying hospitalization and further inconveniences for the patient, plus costs and the risk that resistances against antibiotics develop [12]. Risk stratification and risk-adapted treatment in order to minimize such overtreatment are established in adult oncology [13,14]. In pediatric oncology, the feasibility, cost-effectiveness, efficacy, and recently as well safety of stepping down from inpatient intravenous antibiotics to outpatient oral antibiotics in low-risk FN have been proven [7,15-18]. A range of different clinical decision rules

defining low-risk FN are used in pediatric oncology [19,20]. Their clinical application, supported by recent guidelines is increasing, though still not standard in the majority of pediatric oncology institutions [7,21]. Complete withholding of antibiotics in low-risk FN has been studied in a small proof-of-principle trial [22].

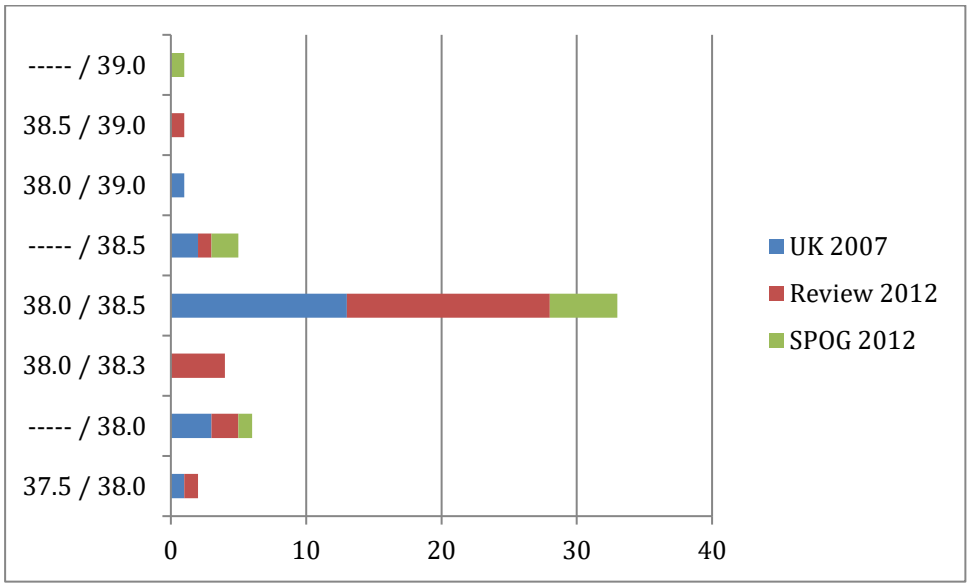
Restricting the definition and the diagnosis of FN by using higher temperature limits defining fever (TLDF), or lower limits of the absolute neutrophil count (ANC) defining neutropenia, inherently has an ever larger potential to reduce overtreatment than the risk-adapted approach mentioned: If the diagnosis of FN is not made, e.g., by spontaneous temperature decrease before the TLDF is reached, the patient is not hospitalized for FN and not treated with empirical antibiotics at all [23,24]. On the other hand, high and very high temperatures are associated with AE in pediatric FN [7,19]. Increasing the TLDF may thus be associated with a relative but as well an absolute increase of AE, essentially by delaying FN diagnosis, and thus start of empirical antibiotics [25].

Conversely, lowering the TLDF or increasing the ANC limit defining neutropenia may lead to additional diagnoses of FN on the one side, and to earlier diagnosis on the other side, with the potential to reduce AE.

3.1.2 TLDFs currently used to define FN

Despite the important implications on the diagnosis of FN, the TLDF, and thus the definition of FN, vary relevantly between different pediatric oncology institutions, even within the same country. In 21 institutions in the United Kingdom (UK), definitions of fever ranged from a persisting temperature of ≥37.5°C as determined by multiple measurements to a single measurement of ≥39°C in 2007 (see Figure 3.1) [12]. The identical range of temperature limits was observed when combining information from 28 original reports on prospective and retrospective studies in pediatric FN, published from 2010 to 2012 and recently reviewed [26] (unpublished data). The 9 pediatric oncology institutions that are members of the Swiss Pediatric Oncology Group (SPOG) were surveyed in January 2012, and they reported a range from a single measurement of ≥38.0°C to a single measurement of ≥39.0°C (unpublished data).

Figure 3.1. TLDFs used clinically and in research
(x-axis, number of centers; from ref. [23], modified)



In all three surveys the majority of fever definitions consisted of either a single measurement of ≥38.5°C or repeated measurements of ≥38.0°C ("38.0 / 38.5" in Fig. 3.1). This combined definition exactly matches the definition in the current European guidelines for adult FN (38.0/38.5°C), and is very similar to the definition in the corresponding U.S. guidelines (38.0/38.3°C) [27,28]. Recent evidence-based pediatric FN guidelines did not cover the question of the TLDF [7]. And in a recent consensus paper on FN research, no consensus for the TLDF in FN could be reached among an

international expert panel of 43 clinicians, pharmacists, researchers and parent representatives interested in FN research [29].

3.1.3 ANC limits defining neutropenia for FN

In contrast to these wide variations in the TLDF, the definition of neutropenia is nearly unanimous for both pediatric and adult FN: A peripheral blood ANC <0.5 G/L defines (severe) neutropenia. This definition is sometimes supplemented by either a leukocyte count <1.0 G/L if a differential leukocyte count is not done, or an ANC <1.0 G/L suspected to fall [28].

In the expert panel mentioned above, there was no consensus reached for the definition of neutropenia neither. The majority of panel members, however, defined neutropenia as an ANC <0.5 G/L, or an ANC <1.0 G/L and expected to decline to <0.5 G/L in the next 48 hours [28,29].

3.1.4 Methods to measure temperature in pediatric oncology

Ear temperature, measured by infrared tympanic thermometry, was shown to reliably and better (though not optimally) reflect core temperature (mean difference, -0.09 ± 1.23°F) than axillary (-1.17 ± 1.13°F) and rectal or forehead measurements during increasing temperature, as well as during steady-state and decreasing temperature [30-32]. Results of ear temperature measurements are thus estimated to be around 1.08°F = 0.6°C higher than results of axillary measurements.

In the three temperature limit surveys mentioned (see 3.1.2), temperature measurement methods were not recorded in the 21 UK institutions [12] (personal communication, B. Phillips), the majority (16 of 28) of recent original publications on pediatric FN did not mention the method used [26] (unpublished data), and the majority (5 of 9) of SPOG institutions used different measurement methods in parallel (unpublished data). In everyday practice, the differences of results implied by using different methods are thus usually neglected. This may bias results in FN research, and thus may interfere with comparisons between centers, and with results of multi-center studies if not both the TLDF and the method of temperature measurement are standardized.

3.1.5 The impact of different TLDFs in FN: safety versus efficacy

The choice of TLDF directly influences whether FN is diagnosed or not. The TLDF has thus important implications on individual patient management, health-related quality of life, resource utilization, costs, and potentially treatment-related mortality [16,17]. The choice of the optimal TLDF must weigh efficacy against safety. Emphasizing efficacy favors a high TLDF in order to avoid FN diagnoses in patients without relevant infections who will spontaneously defervesce, thus finally avoiding overtreatment [23,24]. Emphasizing safety favors a low TLDF in order to avoid delays in FN diagnosis and in start of empirical therapy. Such delays may increase morbidity and lethality in patients with bacterial infection [25].

3.2 Clinical evidence to date

3.2.1 Literature search

A multi-modal search was performed on November 11, 2014, aiming to find published results of past or current research on the optimal TLDF for FN, on the effect of changing this TLDF, and on related topics.

Search strategies used:

1. Literature search in PubMed with 3 combinations of search terms:
    - (fever OR febrile) AND (neutropenia OR neutropaenia) AND (definition OR limit), 146 records screened, 1 relevant publication [23].
    - fever limit AND cancer, 99 records screened, 1 relevant publication [23].
    - fever definition AND cancer, 79 records screened, 1 relevant publication [23].
2. Search for ongoing or past prospective clinical trials on www.clinicaltrials.gov, using 7 different

combinations of search terms:

- fever AND definition AND cancer, 58 records screened, 1 relevant project found [24].
- fever AND definition AND neutropenia, 27 records screened, 1 relevant project found [24].
- fever AND limit AND cancer, 57 records screened, 1 relevant project found [24].
- fever AND limit AND neutropenia, 25 records screened, 1 relevant project found [24].
- temperature AND limit AND cancer, 37 records screened, 1 relevant project found [24].
- temperature AND limit AND neutropenia, 8 records screened, 1 relevant project found [24].
- fever AND neutropenia AND cancer, 165 records screened, 1 relevant project found [24].

In sum, this search found no retrospective or prospective research project studying these topics in adult or pediatric FN, besides the two studies initiated by the Study Chair himself in Bern, Switzerland [23,24].

3.2.2 Retrospective study in Bern and Zurich, 2004-2011

In this retrospective two-center cohort study, 783 FN episodes occurring in 521 pediatric patients with cancer during 6009 months (501 years) of cumulative chemotherapy exposure time (CET) were studied [23]. Three different TLDFs had been used clinically during the 8 years studied: ear temperature ≥38.5°C persisting ≥2 hours (low, Zurich, 2004 to 2011), axillary temperature ≥38.5°C ≥2 hours or ≥39.0°C once (middle, Bern, 2004 to 2007), and ear temperature ≥39.0°C once (high, Bern, 2007 to 2011). Mixed Poisson regression, with CET as rate multiplier, and with a random intercept per patient, was used for analysis [23].

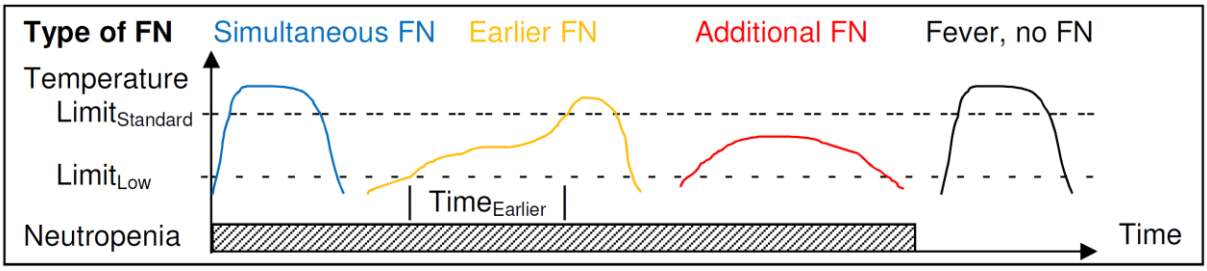
Regarding efficacy, FN rates per month of CET were 0.15 (95% CI, 0.13 to 0.16) for the low TLDF, 0.13 (95% CI, 0.11 to 0.15) for the middle TLDF, and 0.10 (95% confidence interval [CI], 0.08 to 0.11) for the high TLDF. Comparison of the high versus low TLDF resulted in a univariate rate ratio of 0.66 (95% CI, 0.45 to 0.97; p = 0.036). This finding of efficacy of the high versus low TLDF was not confirmed in multivariate analysis, accounting for diagnostic group, myelosuppressive intensity of chemotherapy, and bone marrow involvement (rate ratio, 0.94; 95% CI, 0.67 to 1.33; p = 0.74). This counter-intuitive result of no efficacy of a high TLDF was discussed to potentially be a false negative finding due to methodological limitations of the retrospective study design [23].

Regarding safety, the high versus low TLDF was not associated with an increased rate of FN with bacteremia in univariate (rate ratio, 0.77; 95% CI, 0.25 to 2.37; p = 0.65) and multivariate (rate ratio, 1.39; 95% CI, 0.53 to 3.62; p = 0.50) analyses [23].

3.2.3 Pediatric FN Definition 2012 Bern

This small prospective single-center observational study (NCT01683370) was designed to assess only the efficacy, but not the safety, of the high TLDF used as clinical standard in Bern (ear temperature ≥39.0°C once, called $Limit_{Standard}$ in the manuscript) [24]. It studied 43 FN episodes occurring in 39 pediatric patients with cancer during 289 months of cumulative CET from 2012 to 2013. It simulated different lower TLDFs (called $Limit_{Low}$) *in silicon*, and compared these with $Limit_{Standard}$. This comparison resulted in three types of FN: simultaneous FN, diagnosed at both TLDFs within 1 hour; earlier FN, diagnosed >1hour earlier at $Limit_{Low}$; and additional FN, not diagnosed at $Limit_{Standard}$ (see Figure 3.2). Again, mixed Poisson regression with CET as rate multiplier, and with a random intercept per patient, was used for analysis [24].

Figure 3.2. Types of FN diagnoses applying a low versus high TLDF
(from ref. [24])



Regarding efficacy, the FN rate observed in reality was 0.15 per month (95% CI, 0.11 to 0.20). In 32 (74%) of the 43 FN episodes, $Limit_{Standard}$ had been reached. For clinical reasons, 11 (26%) FN episodes were diagnosed and treated at lower temperatures. In contrast, FN was not diagnosed twice despite fever ≥39.0°C during severe neutropenia. Virtually applying $Limit_{Standard}$ thus resulted in 34 (32 + 2) FN diagnoses. The predefined efficacy measure of a relevantly (≥15%) increased FN rate was reached at $Limit_{Low}$ 38.4°C, with totally 44 FN, 23 of them simultaneous, 11 earlier, and 10 additional (Poisson rate $ratio_{Additional/Standard}$, 0.29; 95% lower confidence bound, 0.16). In 9 of the 10 additional FN episodes spontaneous temperature decrease without specific therapy was observed in reality. Applying an alternative $Limit_{Low}$ of 38.5°C resulted in 41 FN, 24 of them simultaneous, 10 earlier, and 7 additional [24].

Regarding safety, no definite conclusions were possible, because this study was not powered for safety. Combining information from indirect safety-related findings (relevant numbers of FN diagnosed below $Limit_{Standard}$, and of earlier FN), it was concluded that a TLDF of 39.0°C as used in Bern might prove unsafe in larger studies. The fact that the responsible PHO was free to diagnose FN below $Limit_{Standard}$ for clinical reasons lessened this risk [24].

3.2.4 Summary

As detailed above (see 3.1.2, 3.1.4, 3.1.5), there is no consensus on the optimal choice of TLDF weighing efficacy (no overtreatment, high TLDF) against safety (no adverse events, low TLDF) [7,29]. This reflects the fact that currently there is insufficient evidence how to rationally determine an optimal TLDF, balancing the risks of overtreatment versus efficacy and safety, in pediatric oncology. Specifically, a high TLDF of 39.0°C ear temperature has been recently shown to be efficacious when compared to lower temperatures around 38.5°C. It remains open, however, if this high TLDF is as well safe, i.e., if it does not lead to an increased rate of FN with safety-relevant events (SRE). The fact that the responsible PHO is free to diagnose FN below the TLDF for clinical reasons lessens this potential safety risk [24].

3.3 Explanation for choice of TLDFs to be compared

The high TLDF (39.0°C) is the current standard in Bern for all patients except those with acute myeloid leukemia (AML). The low TLDF (38.5°C) is the current standard for patients with AML in Bern, and for all patients in the vast majority of other SPOG sites. The efficacy of the high versus low TLDF has been recently shown, see 3.2.3 [24].

3.4 Risks and benefits

Study participation of non-AML patients treated in Bern (current standard, high TLDF of 39.0°C) will lead to a higher rate of telephone calls by the parents throughout the study (see 9.2.1), and to a higher rate of FN diagnoses when the low TLDF is currently active (see 9.2.2). This is considered to be a small drawback regarding more frequent hospitalization for FN, with a small risk to acquire a nosocomial infection. Should the high versus low TLDF prove to be inferior regarding safety, study participation for these patients will increase safety when the low TLDF is currently active.

Study participation of AML patients treated in Bern, and of all patients treated in the vast majority of other SPOG sites (current standard, low TLDF of 38.5°C) will not influence the rate of telephone calls

throughout the study (see 9.2.1), but to a lower rate of FN diagnoses when the high TLDF is currently active (see 9.2.2). This is considered to be a benefit. Should the high versus low TLDF prove to be inferior regarding safety, however, study participation for these patients will decrease safety regarding FN treatment when the high TLDF is currently active. It is yet known that this potential decrease in safety is not big, however [23,24].

Interim analyses are planned to reduce the risks mentioned above by allowing early stopping of the study both for success (non-inferiority proven) or for futility (non-inferiority not provable) (see 11.4.6)

In sum, the potential risks and benefits for patients participating in the study seem to be acceptable and well-balanced.

The main benefit of this study is the increase in knowledge, aiming at precision medicine in this context. This will help to optimize the future treatment of only a small minority of study participants, but of a large number of children and adolescents treated with chemotherapy for cancer in the future: If this study shows evidence of non-inferiority of a high versus low TLDF regarding safety this high TLDF can be used clinically in pediatric oncology centers in developed countries. This will lead to a reduction in the current overtreatment of pediatric FN, by reducing over-diagnosis. If there is no evidence of non-inferiority, however, centers currently using this high TLDF should revise their clinical practice.

3.5 Justification of choice of study population

FN in children and adolescents is known to differ in many core characteristics from FN in adults [7]. This is the reason why the aims of this study can be reached only by the study of children and adolescents themselves despite them being especially vulnerable study participants. See 2.7 for information on the corresponding implications on the informed consent process.

4. STUDY OBJECTIVES

4.1 Overall objective

The overall objective of this study is to determine the safety and efficacy of a high versus low TLDF, for the definition of FN, in children and adolescents with cancer treated with myelosuppressive (not myeloablative) chemotherapy.

4.2 Primary objective

The primary objective is to determine if a high TLDF is non-inferior to a low TLDF regarding safety.

4.3 Secondary objective

The secondary objective is to determine if a high TLDF is superior to a low TLDF regarding efficacy.

4.4 Tertiary objective

The tertiary objective is to make use of the data collected for development of risk prediction rules, and for external validation of published risk prediction rules.

5. DEFINITIONS AND STUDY OUTCOMES

5.1 Definitions

5.1.1 Temperature measurement method and device, fever, and TLDFs

Throughout the study, all temperatures are measured as ear temperatures by infrared tympanic thermometry using a Braun ThermoScan® 7 device (IRT 6520; Braun GmbH, Kronberg, Germany; steps displayed, 0.1°C; accuracy, ±0.2°C; clinical repeatability,±0.14°C) [24,30-33], or its successor device with comparable or better performance characteristics. All parents are trained in the correct use of this device at study entry.

Fever is defined as a single ear temperature at or above the current TLDF.
The TLDFs used in this study are 38.5°C (low TLDF), and 39.0°C (high TLDF; see 8.1).

5.1.2 Severe chemotherapy-induced neutropenia

Severe chemotherapy-induced neutropenia (called neutropenia here) is defined as an ANC <0.5 G/L, or an ANC <1.0 G/L and expected to decline to <0.5 G/L in the next 48 hours [28,29]. Neutropenia can be diagnosed from the start of chemotherapy until 21 days after the last dose of chemotherapy. The additional 21 days account for neutropenia, and thus risk of FN, developing after cessation of chemotherapy [4].

5.1.3 Types of clinically defined FN episodes

A clinically defined FN episode (FN_{Clin}) is defined as an episode of at least slightly elevated temperature (≥38.0°C) and severe neutropenia, during which the responsible local PHO diagnoses FN, and/or starts FN therapy (including but not restricted to emergency hospitalization for outpatients, plus empirical intravenous antimicrobial therapy). In rare exceptions, to be discussed individually with the Study Chair / Study Vice Chair, this limit can be further lowered to 37.5°C in patients repeatedly receiving antipyretics despite neutropenia, a practice strongly discouraged by this protocol.

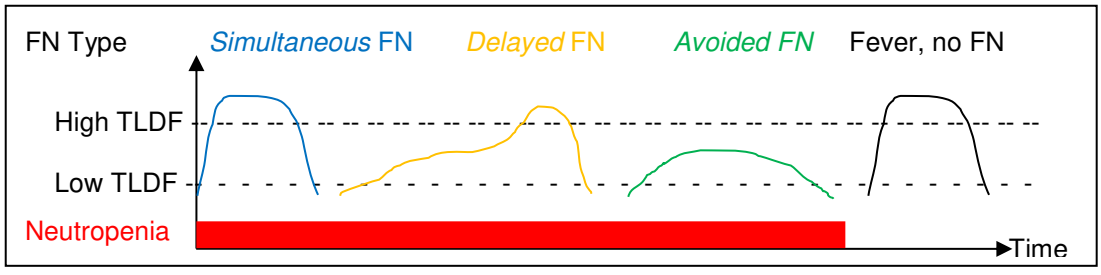
An FN_{Clin} can thus be diagnosed at/above the currently effective TLDF for a specific patient (then called FN_{TLDF}), or below this TLDF (then called FN_{Below}). This definition reflects the fact that the responsible local PHO is always free to diagnose FN and treat the patient correspondingly for clinical reasons even if the TLDF is not reached (see 8.2) [24].

The temperature used for defining FN_{Clin}, and for distinguishing between FN_{TLDF} an FN_{Below}, is the first temperature at or above the currently active TLDF for FN_{TLDF}, or the highest temperature reported by the patients or parents, or measured at presentation with FN, before the start of empirical antimicrobial therapy for FN_{Below} [6].
The TLDF currently active at the time when this temperature defining FN_{Clin} is measured determines TLDF linked to this FN_{Clin} for analysis.

5.1.4 Types of FN episodes comparing high versus low TLDF

When the high TLDF is currently active, the comparison with virtually applying the low TLDF results in three types of FN (see Fig. 5.1, ref [24]): Simultaneous FN is diagnosed without relevant delay (≤1 hour) from passing the low TLDF. Delayed FN is diagnosed with a relevant delay (>1 hour and ≤168 hours) from passing the low TLDF, with continued neutropenia and continued fever (temperature measured at least once ≥38.0°C every 24 hours) during this delay time. Avoided FN diagnosis is defined by temperature passing the low, but not the high TLDF, within a timeframe of ≤168 hours with continued neutropenia and continued fever (temperature measured at least once ≥38.0°C every 24 hours) [24].

Figure 5.1. Types of FN diagnoses applying a high versus low TLDF (modified from [24])



5.1.5 Duration of FN episodes

The duration of antimicrobial therapy for FN defines the duration of FN episodes. Restarting antimicrobial therapy within 7 days and with persistent neutropenia is considered to belong to the same FN episode. Start of intravenous chemotherapy immediately ends an FN episode, overruling the

preceding definition. Correspondingly, all outcomes are tracked onward for 7 days after the end of antimicrobial therapy for FN, as long as neutropenia persists and intravenous chemotherapy has not been started [6,24].

5.1.6 Chemotherapy intensity

Chemotherapy is classified into four levels of intensity according to the expected duration of severe neutropenia [4,34]:

- Intensity 1: no severe neutropenia expected (e.g., maintenance therapy for acute lymphoblastic leukemia)
- Intensity 2: severe neutropenia expected ≤10 days (e.g., therapy for most solid tumors)
- Intensity 3: severe neutropenia expected >10 days (e.g., non-maintenance therapy for AML)
- Intensity 4: myeloablative chemotherapy, hematopoietic stem cell therapy required

The study center will verify reported chemotherapy intensities (see 12.2.4).

5.1.7 Chemotherapy exposure time

The CET equals the length of study participation of a specific patient, and refers to myelosuppressive (intensity 1 to 3), but not to myeloablative chemotherapy (intensity 4). The start is the day of the first dose of chemotherapy (or of recruitment into the study, whichever comes later). The end is 21 days after the last dose of chemotherapy (or end of study for other reasons, whichever comes earlier; see 5.1.2) [4].

5.1.8 Safety-relevant event

A composite endpoint is chosen for the primary outcome [29,35,36]. Specifically, a safety relevant event (SRE) is defined as bacteremia detected, and/or a serious medical complication (SMC) reported.

Bacteremia is defined according to a recent consensus definition [29,37] as the culture of a recognized pathogen from one or more blood cultures (includes viridans group streptococci in the setting of concomitant mucosal barrier injury). Common commensals should be cultured from two or more blood cultures drawn on separate occasions. Where only a single blood culture is taken, and in the presence of a long term vascular catheter, common commensals cultured once may be included if an alternative source of infection is not identified. (Blood cultures drawn from different sites including different venepunctures or different lumens of the same central line, should undergo separate decontamination and are therefore considered drawn on "separate occasions." A complete list of common commensals is available via the online Centre for Disease Control and Prevention resource [37]).

In this study, it is not required to draw blood cultures from venepunctures in addition to blood cultures drawn from central lines.

A serious medical complication is defined according to a recent consensus definition [29] as

- death due to any cause during FN [modified from ref. 29], or
- admission to 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 [38]

In view of these non-trivial definitions, the study center will verify SREs and potential SREs reported by the study sites (see 5.2, 12.2.4).

5.2 Primary outcome and its assessment

The primary outcome is the Poisson rate of FN_{Clin} with at least one SRE per CET. It is assessed per patient during the entire study duration in patient charts, and reported monthly by the study sites to the study center. The study center verifies the SRE status of FN episodes (see 5.1.8, 12.2.4).

The primary outcome refers to SRE during FN_{Clin}, not during FN_{TLDF}. Reporting only FN_{TLDF} with SRE as events would lead, by definition, to non-reporting of FN_{Below} with SRE, which would not reflect clinical reality. This underreporting would be, again by definition, more important for the high TLDF than for the low TLDF. This bias would thus finally lead to a falsely low rate ratio , with the

risk of falsely declaring the high TLDF as safe.

5.3 Secondary outcomes and their assessment

The secondary safety-related outcomes are

A. Times (hh:mm) of measurement of fever – telephone to study site – arrival at emergency department – prescription of antibiotics – start and end of first dose of i.v. antibiotics (assessed per FN episode by the responsible local PHO and in patient chart, reported per FN episode)

B. AE: clinically / microbiologically documented infection, unexplained fever, sepsis / severe sepsis / septic shock, relapse of primary infection (definitions see refs. 29, 38; assessed in patient charts, reported per FN)

C. Only for currently active high TLDF: delay time between crossing low and high TLDF; delayed FN diagnosis (see 5.1.4) by high vs. low TLDF (assessed from patients charts, reported per FN)

The secondary efficacy-related outcomes are

D. Poisson rate of FN_{Clin} per CET (assessed like primary outcome; main measure of efficacy)

E. Poisson rate of FN_{TLDF} and FN_{Below} per CET (assessed like primary outcome)

F. Duration (days) of hospitalization, ICU treatment, i.v. antibiotics, p.o. antibiotics, any antibiotics, delay of chemotherapy for FN (assessed in patient charts, reported per FN episode)

G. Only for currently active high TLDF: simultaneous and avoided FN diagnosis (see 5.1.4) by applying high vs. low TLDF (assessed from patients charts, reported monthly and per FN)

6. STUDY DESIGN

6.1 General study design and justification of design

This is a multi-center open-label cluster-randomized controlled parallel-group multiple-crossover non-inferiority trial, with study sites as units of randomization, and patients as units of analysis.

Every month, 1:1 randomizations between the two different TLDFs are repeated for each study site. This implies that the TLDF is identical for all study participants within each study site. Per-site instead of per-patient randomization was chosen for practical reasons, aiming to reduce assignment errors due to the repeated changes in the currently active TLFD. This leads to potential multiple cross-overs within patients. This scheme was chosen in order to decrease the target number of events (FN_{Clin} with SRE; see 5.2, 11.2), and thus the number of patients needed thanks to the increase in power reached by within-patient cross-over.

6.2 Methods of minimizing bias

6.2.1 Randomisation

See 7.4.

6.2.2 Blinding procedures

None, this is an unblinded study.

6.2.3 Other methods of minimizing bias

- Uniform method and device for temperature measurements (see 5.1.1).
- Verification of chemotherapy intensity and SREs by study center (see 5.1.6, 5.1.8, 9.3.1).
- Use of clinically defined FN (FN_{Clin}) with SRE as primary outcome (see 5.3).
- Use of mixed Poisson regression for analysis of primary and other outcomes (see 11.4.1).
- Analysis in the per protocol (PP) set for primary outcome (see 11.4.2) [39].

7. STUDY POPULATION

7.1 Requirements for study sites

Study sites must fulfill all of the following requirements:

- Member institution of SPOG
- Consistent temperature measurement method at home, in outpatients and inpatients: ear, infrared tympanic thermometry (see 5.1.1)
- Simple single TLDF (see 5.1.1)
- Empirical FN therapy: ≥1 dose i.v. antibiotics (see 9.2.3)
- Rules for diagnosis and management of FN predefined in standard operating procedure (SOP) or SOP-like documents (e.g., standard prescription, flowsheet).
- Board-certified pediatric oncologist on call 24 hours per day, 365 days per year
- Access to pediatric ICU
- Willingness to perform the study according to the protocol

7.2 Eligibility criteria for patients

Patients fulfilling all of the following inclusion criteria are eligible for the study:

- Chemotherapy treatment because of any malignancy planned for at least 2 further months at time of recruitment for myelosuppressive therapy, or at least 1 cycle of myeloablative chemotherapy followed by autologous hematopoietic stem cell transplantation
- Age ≥12 months and <18 years at time of recruitment
- Written informed consent from patients and/or parents, as documented by signature (see 2.6)

The presence of any one of the following exclusion criteria will lead to exclusion of the patients:

- Infants <12 months (reason: difference in temperature measurement method)
- Past allogeneic hematopoietic stem cell transplantation
- Denied written informed consent from patients and/or parents (see 2.6)

Reason for inclusion of children/adolescents (vulnerable participants): important differences in core FN characteristics between children/adolescents and adults [7].

7.3 Screening and recruitment

Patients of the study sites are screened for eligibility and recruited by the teams of these sites. No specific screening procedures except verifying inclusion/exclusion criteria are needed. See Appendix A for a list of study sites.
There will be no advertisements, and no payment given to study participants.

7.4 Assignment to study groups

See 6.1 for basic information on randomized allocation of patients, via monthly repeated 1:1 randomization of study sites, to the two different TLDFs (see 8.1).
A randomization sequence covering 72 months is generated at study entry of each study site by the study center using computer-generated random numbers. These sequences are stored in the study center. In the middle of each month, the study center informs the study sites on the TLDF assignment of the next month, valid for all patients of the respective site.
The TLDF thus changes over time for the study site, and thus as well for most of the patients. The currently active TLDF will decide on the clinical procedures to be performed (see 9.2.2).

7.5 Criteria for withdrawal / discontinuation / end of study of patients

Patients are withdrawn from the study in case of withdrawal of informed consent, and when study participation is not in the best interest of the patient any more, including relevant non-compliance, as judged by the study site or the study center. The study ends regularly when patients have reached the age of 20 years, at the end of the study as such, at the first day of myeloablative chemotherapy before allogeneic hematopoietic stem cell transplantation, 21 days after the last dose of chemotherapy, or at

the day of death from any cause.

See 8.3 for follow-up, data collection and use of data for withdrawn patients.

8. INTERVENTION

8.1 Intervention: temperature limit defining fever

A distinction into a standard and an experimental intervention is not possible, because both TLDFs are in clinical use today (see 3.1.2).
Two TLDFs used in this study are 38.5°C (low TLDF), and 39.0°C (high TLDF; see 5.1.1). See 7.4 for assignment to study groups, and see 9.2.2 for the clinical procedures performed according to the currently active TLDF.

8.2 Compliance with study intervention

The Sponsor will perform risk-adapted monitoring.
Non-compliance apparent during monitoring or audit visits will be handled according to SPOG Office SOPs. The Study Chair informs the Sponsor about any non-compliance observed.
Making a FN_{Below} diagnosis is not considered to be a protocol violation (see 9.2.2).

8.3 Data Collection and Follow-up for withdrawn participants

No specific follow-up beyond the date of withdrawal (see 7.5) is performed. No data will be collected beyond the date of withdrawal. The information collected until this date will be used for analysis. This information will be fully anonymized after analysis (see 12.2.3).

9. STUDY PROCEDURES AND ASSESSMENTS

9.1 Assessment of eligibility

Eligibility of patients, according to inclusion and exclusion criteria (see 7.2) is assessed during a routine outpatient visit, or during routine hospitalization. Each study site assesses the eligibility of all patients treated at the site with chemotherapy. Coded information on sex, year of birth, diagnostic group, participation or reason for non-participation, and date of assessment of all these patients is transmitted to the study center via partial copies of the patient screening log.

9.2 Mandatory clinical procedures throughout the study

The minimally required clinical procedures described below can be supplemented by additional procedures specific to the study site. Such additional procedures must not interfere with the minimally required clinical procedures, and they must not make distinctions between the two TLDFs. The minimally required and the additional procedures are described in a FN SOP or SOP-like document specific for each study site (see 7.1).

The requirements for patients and/or parents (see 9.2.1) are additionally described in the respective information documents (see 17.2).

9.2.1 Mandatory procedures by patients and/or parents throughout the study

In outpatients, the ear temperature is measured if fever is suspected (see 5.1.1 for technical details) [40]. If a temperature ≥38.5°C (low TLDF) is measured, or if the patient's general performance is reduced, the responsible local PHO is immediately informed via the study site.

In inpatients, the nurses act correspondingly.

Parents are not obliged to document results of temperature measurements. Besides, it is not usually clinically needed to know the exact (as required here for secondary outcome A) results and time points of temperature measurements reported by parents. Thus, they are not reliably documented in patients' charts. This is the reason why the exact results and time points of relevant temperature measurements

(first temperatures ≥38.0°C, ≥38.5°C, and ≥39.0°C, respectively) made by parents are directly noted on the respective CRF. Measurements of inpatients and outpatients, however, are reliably and exactly noted in patients' charts.

9.2.2 Mandatory procedures by the responsible local PHO in case of reported fever

When the responsible local PHO knows of a patient with ear temperature ≥38.5°C (low TLDF), and/or with reduced general performance, he/she decides if an emergency complete blood count (CBC) must be performed in order to assess a potential neutropenia (last CBC >48 [72 in unequivocal situations] hours old, or suspected not to reflect the current ANC).

In case of neutropenia and an ear temperature at or above the currently active TLDF (38.5°C, or 39.0°C), FN must be diagnosed (FN_{Clin}, specifically FN_{TLDF}) (see 9.2.3 for further procedures).

In case of neutropenia and an ear temperature below the currently active TLDF, FN is not routinely diagnosed, thus no antibiotics and no antipyretics are given. FN can be diagnosed, however, for clinical reasons, if the ear temperature is ≥38.0°C (FN_{Clin}, specifically FN_{Below}, see 5.1.3) (see 9.2.3 for further procedures). Making a FN_{Below} diagnosis is not a protocol violation.

In all other cases, FN is not diagnosed, and all diagnostic and therapeutic measures are at the discretion of the responsible local PHO.

9.2.3 Mandatory procedures at diagnosis of FN

In case of any FN diagnosis (FN_{Clin}: FN_{TLDF} or FN_{Below}), the following procedures must be performed:

- Emergency hospitalization
- Minimum set of observations, including
  - History
  - Physical examination
  - Blood culture from central venous access device (CVAD) to be analyzed in automated system (blood culture from venepuncture only in patients without CVAD)
  - CBC (not to be repeated if performed within 12 hours at the study site),
    International normalized ratio of coagulation, and serum creatinine, total bilirubin, alanine transaminase,
    C-reactive protein
- Emergency start with empirical intravenous broad-spectrum antibiotics (Complete abstention from antimicrobial therapy [22] is not allowed in this study.) This antimicrobial therapy is specified by each study site. It must fulfill the following requirements [6]:
  - It must cover Gram-positive cocci (e.g., *Staphylococcus aureus, Streptococcus pneumoniae*, other streptococci) except methicillin-resistant *S. aureus*, coagulase-negative staphylococci, and enterococci.
  - It must cover Gram-negative bacteriae (e.g., *Neisseria species, Haemophilus species, Moraxella catarrhalis,* enterobacteriaceae*, Pseudomonas aeruginosa*).
  - A specific anti-anaerobic coverage is not needed.
  - It must be adapted to the local resistance patterns.

All further diagnostic and therapeutic measures (e.g. risk-adapted step-down strategies, switching antibiotics, adding antifungals, discharge) are performed according to the SOP or SOP-like documents (see 7.1) specific to the study sites, or at the discretion of the responsible local PHO if they are not covered by this document. The TLDF currently active at diagnosis of FN is as well used for decisions on diagnostics, supportive care incl. antibiotics, discharge, and other aspects depending on fever.

9.3 Assessments of outcomes

See 5.2 for the assessment of the primary outcome, see 5.3 for assessment of the secondary outcomes, and see 5.2, 5.3 and 10 for the assessment of safety outcomes.

10. SAFETY

Regarding safety, serious adverse event (SAE) reporting is used in parallel to the assessment and analysis of the primary outcome and a set of secondary outcomes (see 9.2.1, 9.2.2).

10.1 Definition of serious adverse events

A SAE is defined here as any untoward medical occurrence, occurring during a FN_{Clin} episode, that

- results in death,
- is life-threatening,
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

This definition is more restrictive than the general SAE definition [2] for two reasons: First, as every FN leads to hospitalization of undetermined length (see 9.2.2), the usual criterion of "requirement of in-patient hospitalization or prolongation of existing hospitalization" is not used as a criterion defining SAE in this study. Second, since the intervention in this study has potential implications on the time of FN diagnosis, but not on any aspect outside of FN, SAEs are restricted in this study, by definition, to events occurring during FN_{Clin} (see 5.1.5).

Any event caused by progression of the underlying malignancy is not considered as SAE. In case of doubt, the investigator contacts the Study Chair.

10.2 Reporting of SAE

Every SAE must be documented and reported within 7 days (using the SAE form) by the study sites to the SPOG Office (safety@spog.ch) with a copy to the Study Chair (roland.ammann@insel.ch) and the Study Vice Chair (nicole.bodmer@kispi.uzh.ch) [2]

An SAE for which a relationship with the intervention studied here cannot be excluded must be documented and reported within 24 hours (using the SAE form) by the study sites to the SPOG Office (safety@spog.ch) with a copy to the Study Chair (roland.ammann@insel.ch) and the Study Vice Chair (nicole.bodmer@kispi.uzh.ch) [2].

Deaths during ongoing SAEs have to be reported within the same timelines specified above (24 hours or 7 days, respectively).

Upon receipt of an SAE form the SPOG Office informs the Study Chair/Study Vice Chair about the reported SAE (double check). The Study Chair/Study Vice Chair checks SAE reports for medical consistency and for completeness, sends the respective queries to study sites where needed, and performs a plausibility check of the relatedness of the SAE to the intervention studied in this study. If a relatedness of the SAE to the intervention studied cannot be excluded the Sponsor informs the lead CEC and the respective local CEC on all SAEs within 15 days [2]. If Sponsor and Study Chair / Study Vice Chair cannot resolve discrepancies regarding the question of such relatedness, an external expert is asked for advice.

Clinical follow-up after an SAE is performed as part of the clinical routine by the respective study site.

10.3 Annual Safety Report

The Study Chair writes an annual safety report (ASR) in cooperation with the SPOG Office. This report follows the standards for the executive summary defined by the ICH Guideline E2F supplemented with a line listing of all SAEs for which a relation with the intervention studied here cannot be excluded which have occurred during the reporting period of this ASR, and during the entire study. The yearly cut-off date refers to the date the study was approved by the leading CEC. The SPOG Office submits this report to the concerned local CECs, the leading CEC, and additionally to all involved PIs within 90 days from this yearly cut-off date.

10.3 Further safety issues

If immediate safety and protective measures have to be taken during the conduct of the study, the Study Chair informs all participating PIs and the Sponsor immediately of these measures, and of the circumstances necessitating them. The Sponsor will notify the CECs of any safety issue within 7 days. See 11.3 regarding occurrence of deaths.

11. STATISTICAL METHODS

11.1 Hypothesis for the primary objective / primary outcome

Statistical null hypothesis (H_0): The rate ratio of FN_{Clin} with SRE (primary outcome for safety) is not non-inferior (non-inferiority margin 1.33) for a high versus low TLDF. The non-inferiority-margin is chosen more conservatively than the suggested de-facto standard of 1.50 [41] because the primary outcome is a safety outcome.
Statistical alternative hypothesis (H_1; corresponds to the clinical hypothesis, see 3.1, 4.2): The rate ratio of FN_{Clin} with SRE (primary outcome for safety) is non-inferior (non-inferiority margin 1.33) for a high versus low TLDF.

11.2 Determination of sample size and study duration

Sample size calculations and thus decisions when to perform interim and final analyses refer to events regarding the primary outcome, i.e., FN_{Clin} episodes with SRE (see 5.1). The number of events needed was determined by a series of 1000-fold random simulations, applying mixed Poisson regression on a set of retrospective data on 1164 FN episodes in 898 patients treated with myelosuppressive (but not myeloablative) chemotherapy in two centers, Bern 1993-2012, and Zürich 2004-2011 [4,23,42]. Specifically, the glmmPQL function from the nlme package in the MASS library [43] was used for mixed Poisson regression simulations in R 3.1.2 [44].

Assuming an event rate ratio of 1.05 for high versus low TLDF, and applying monthly repeated randomization within patients leading to multiple crossover, a sample size of 116 events was found to yield a power of 80% (beta = 0.20) at alpha = 0.05 to detect non-inferiority. Accounting for the 3 interim analyses (see 11.4.4) leads to a target sample size of 132 events (FN_{Clin} with SRE) [45].

Assuming that SRE will occur in 24% of FN_{Clin} [9], these 132 events of FN_{Clin} with SRE correspond to approximately 550 FN_{Clin} episodes in total. Assuming a rate of 1.48 FN_{Clin} episodes per year of CET [4,23], these 550 FN_{Clin} episodes correspond to approximately 372 years of CET. It is assumed that SPOG institutions treating in total 2/3 of the pediatric cancer patients diagnosed in Switzerland will participate, and that 2/3 of the patients potentially eligible are recruited. Then, around 100 of the 220 newly diagnosed and around 10 of the 20 relapsed pediatric cancer patients diagnosed in the annual mean in Switzerland [46] will be recruited per year. This corresponds to around 110 years of CET per year [1], resulting in an estimated study duration of 3.5 years after a 3 months run-in phase (see Table 11.1).

Table 11.1. Planned timetable (assuming study is not stopped at interim analyses, see 11.3, 11.4.4)

2015, June	Submission to pediatric IRB Bern
2015, December	Submission to CECs
2016, February	Setting up study center, start initiating study sites
2016, March	Recruitment of first patient
2016, June	End of run-in phase of patient recruitment
2017, April	Accrual for first interim analysis reached: 33 events of FN_{Clin} with SRE
2018, February	Accrual for second interim analysis reached: 66 events of FN_{Clin} with SRE
2018, December	Accrual for third interim analysis reached: 99 events of FN_{Clin} with SRE
2019, October	Target of 132 events of FN_{Clin} with SRE reached (last patient last visit)

2020, January	Data closure, clean data
2020, April	Data analyzed
2020, October	Manuscript with main results submitted

11.3 Statistical criteria of termination of trial

There are no statistically defined discontinuation criteria for individual participants.

The study itself will be stopped when the boundary for proven inferiority or proven non-inferiority is crossed at an interim analysis (see 11.4.4), or when the target sample size of 132 FN_{Clin} with SRE reported and verified (see 12.2.4) by the study center has been reached.

It is expected that in this study there will be multiple deaths due to FN. In a recent multicenter study on FN in Switzerland and Germany, the proportion of FN with death was 0.7% [9]. If this study is not stopped at an interim analysis, and the target size of 132 FN_{Clin} with SRE is reached, up to 10 deaths are expected (0.7% of 550 FN, see 11.2; corresponding estimate, 4; exact 95% Blyth-Still-Casella CI, 1 to 10). The occurrence of deaths during FN_{Clin} is thus not a reason to stop the study.

11.4 Planned statistical analyses

11.4.1 General strategy of analysis, and datasets to be analysed

For all outcomes, descriptive statistics using standard methods will be performed. For all outcomes except secondary outcomes C and G, analytical statistics will be performed as described below.

Because multiple randomizations are performed per patient, via monthly randomizations of centers, the datasets to be analyzed do not refer to patients, but to randomization periods (maximum length, 1 month) of patients. The intention-to-treat (ITT) dataset contains all periods of patients reported to be on study by a study site on beginning of a month (first day of month, 00.01 AM). The per-protocol (PP) dataset contains all periods of the ITT dataset, for which the study site had informed its pediatric oncology inpatient and outpatient departments and the emergency department on the result of randomization until beginning of the month. Diagnosis of FN_{Below} is possible according to the protocol, and does not lead to exclusion from the PP dataset (see 9.2.2).

Mixed regression analyses, with random intercepts per patient nested within study site (three-level random intercept model) will be used to account for multiple entries / multiple FN per patient [47]. Specifically, mixed Poisson regression with CET as rate multiplier will be used for Poisson distributed events, mixed logistic regression for binary outcomes, and mixed linear regression for continuously distributed outcomes.

If not otherwise stated, two-sided tests will be used, analyses will be performed at the end of the study, and in ITT dataset, p-values <0.05 will be considered significant, and correspondingly, 95% CI will be calculated. The current version of the R software [44] will be used for analysis.

11.4.2 Primary objective safety: Main analysis

The rate ratio of the primary outcome, FN_{Clin} with SRE per CET, for high versus low TLDF (see 5.2, 9.3.1) will be analyzed using univariate mixed Poisson regression (see 11.4.1) in the PP dataset [39] at the end of the study. Past interim analyses will be accounted for in this final analysis [45].
If a significant carry-over is detected (carry-over window of 24 hours after switch from high to low TLDF; mixed Poisson regression on carry-over; $p<0.05$), this univariate analysis is replaced by a bivariate analysis, adjusted for this carry-over effect.
The estimate of the rate ratio and its (one-sided) 95% upper confidence bound (UCB) will be reported. If this UCB is below the non-inferiority margin, i.e., <1.33, non-inferiority of the high versus low TLDF regarding safety will be claimed.
Three sensitivity analyses will be performed: First, a multivariate analysis in the PP dataset, adjusting for chemotherapy intensity, time since diagnosis, bone marrow involvement, type of CVAD and past FN [4]; second, a uni- or bivariate analysis in the ITT dataset; and third, a multivariate analysis in the ITT dataset.

11.4.3 Primary objective safety: Further analyses

Secondary outcomes A: The durations, calculated as differences in time, will be analyzed for high vs. low TLDF by mixed linear regression (see 11.4.1.
Secondary outcomes B: These binary outcomes will be analyzed in two ways for high versus low TLDF: First, by mixed logistic regression (see 11.4.1) to assess differences on the level of FN_{Clin} episodes; and second, by mixed Poisson regression (see 11.4.1) to assess differences on the CET level.

11.4.4 Secondary objective efficacy: Main analysis

The rate ratio of the secondary outcome D, FN_{Clin} per CET for high versus low TLDF, will be analyzed by uni-or bivariate (see 11.4.2) mixed Poisson regression (see 11.4.1) in the ITT set [39]. If the 95% UCB of the rate ratio is below the superiority margin, set at equality, i.e., if it is <1.00, superiority of the high versus low TLDF regarding efficacy will be claimed.
Three sensitivity analyses will be performed: First, a multivariate analysis in the ITT set; second a univariate analysis in the PP set; and third, a multivariate analysis in the PP set.

11.4.5 Secondary objective efficacy: Further analyses

Secondary outcomes E: The rate ratios of FN_{TLDF} and of FN_{Below} will be analyzed like secondary outcome D, FN_{Clin} (see 11.4.4).

Secondary outcomes F: These durations will be analyzed in two ways for high versus low TLDF: First, by mixed linear regression (see 11.4.1) to assess differences on the level of FN_{Clin} episodes; and second, by mixed Poisson regression (see 11.4.1), to assess differences on the level of CET.

Secondary outcome G: The rate ratios of simultaneous FN and of avoided FN will be analyzed like secondary outcome D, FN_{Clin} (see 11.4.4), for periods with high TLDF only.

11.4.6 Tertiary objective, risk prediction rules

Rules predicting the risk to develop FN (FN_{Clin}, FN_{Clin} with bacteremia / SMC /SRE) during chemotherapy will be based on multivariate mixed Poisson regression (see 11.4.1), applying stepwise forward variable selection.
Rules predicting the risk to develop AE (bacteremia / SMC /SRE) during FN will be based on multivariate mixed logistic regression (see 11.4.1), applying stepwise forward variable selection.
The predictive performance of published rules predicting the risk to develop FN (FN_{Clin}, FN_{Clin} with bacteremia / SMC /SRE) during chemotherapy will be assessed by multivariate mixed Poisson regression (see 11.4.1).
The predictive performance of published rules predicting the risk to develop AE (bacteremia / SMC / SRE) during FN will be assessed by multivariate mixed logistic regression (see 11.4.1).

11.4.7 Interim analyses for the primary outcome

For the primary outcome, a Power family scheme of group sequential one-sided tests is used, with a maximum of 3 equally spaced interim analyses, after 33 (25%), 66 (50%), and 99 (75%), events are reached, respectively. Specifically, O'Brian-Fleming-type boundaries defined by delta = 0 are used, with tests both for proven non-inferiority (success) and non-provable non-inferiority (futility) performed at each analysis. This scheme increases the maximum number of events by a factor of 1.140, i.e., from 116 (100%) to 132 (114%). The expected number of events, however, is decreased to 71 (61%) assuming non-inferiority (theta = 0), and to 90 (78%) assuming inferiority (theta = 1) [45].

Table 11.2. Stopping boundaries at interim and final analyses, expressed as z-values

Interim 1 (33 events)	Interim 2 (66 events)	Interim 3 (99 events)	Final (132 events)	Consequence
≥ 3.312	≥ 2.342	≥ 1.912	≥ 1.656	Stop study: proven non-inferiority
-0.671 to 3.311	0.465 to 2.341	1.146 to 1.911	-	Continue study
< -0.671	< 0.465	<1.146	< 1.656	Stop study: non-inferiority not provable

The corresponding stopping boundaries, expressed as z-values, of the interim and final analyses are displayed in Table 11.2 [45]. At interim analyses and, if applicable, at the final analysis (see 11.4.2), z-values are calculated from the results of the univariate or bivariate (see 11.4.2) mixed Poisson regression analysis (see 11.4.1) in the PP dataset as $z = (\ln(1.33) - \text{beta}) / SE_{\text{beta}}$.

11.4.8 Safety analysis

In addition to the analysis of the primary, safety-related outcome (see 11.4.2), and the analyses of the safety-related secondary outcomes (11.4.3), the number, proportion and nature of SAEs (see 10.1) will be reported.

11.4.9 Deviations from the original statistical plan

Deviations from the planned analyses for the primary endpoint and for the secondary endpoints will be justified and described in an amendment of the protocol, if the Study Committee decides so. In any case, deviations from the planned analyses for these endpoints will be described in the corresponding manuscripts if they are decided upon after the recruitment of the first patient.

11.5 Handling of missing data and drop-outs

There will be no imputation for missing data (multiple imputation, last observation carried forward, and alike). No replacement of drop-outs is needed, because the target sample size refers to events, i.e., FN_{Clin} with SRE, not to patients.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

All information collected during the study must be entered in case report forms (CRFs). CRF are completed either by the PI or a designated representative authorized by the PI. Authorisation of any local staff member to make CRF entries must be documented on the according staff list.
Primarily, paper CRFs will be used, later replacement by electronic CRFs is possible.
Study patients are not identified in the CRF by name, initials, or birth date. A combination of site acronym, participant number and year of birth (e.g., BE.001.2003) is used in the CRFs to decrease the risk of patient mistakes.

12.1.2 Specification of source documents

Source documents include the patients' charts, which are stored at the site specific usual location for charts, plus study-specific documents (Informed Consent forms, randomization lists, subject identification logs, and relevant correspondence), which are filed in the Investigator Site File (ISF). The ISF is stored at a different study-specific location defined by the responsible investigator of the study site.

12.1.3 Record keeping / archiving

Source documents as well as the ISF have to be archived at each site for a minimum of 10 years after termination of the study. Each local principal investigator is responsible to archive source documents and the ISF according to site-specific procedures.

The Study Master File is archived at SPOG Office according to the SPOG Office SOP on archiving.

12.2 Data management

12.2.1 Data Management System

A current version of the RedCap software, or a comparable system fulfilling the legal requirements [1,2], will be used for data management at the study center. The Study Chair is responsible for its use. Before entry of the first patient into the study, it is extensively tested using fake data in all CRFs.

12.2.2 Data security, access and back-up

The Study Chair, and persons authorized by him, have access to data.
The data management system chosen has built-in security and back-up functions fulfilling the legal requirements [1,2] (see 12.2.1).

12.2.3 Analysis and archiving

For interim and final analysis, data are extracted using built-in extraction procedures into a form readable by the software used for the statistical analysis (see 11.4.1). After analysis, data of withdrawn patients will be fully anonymized (see 8.3). The data are stored for a minimum of 10 years after termination of the study.

12.2.4 Electronic and central data verification

In the study center, CRFs are checked for completeness and consistency, and the primary outcome (SRE status of FN episodes, see 5.1.8, 5.2) and the chemotherapy intensity (see 5.1.6) are verified. The respective study sites are requested to provide missing information. Discrepancies are discussed with the study sites until resolved, and the written results of these discussions are stored in the study center.
Data are then entered into the data management system (see 12.2.1), in which range checks and further consistency checks are implemented. Again, discrepancies are discussed with the study sites until resolved, and the written results of these discussions are stored in the study center.

12.3 Monitoring

The Sponsor will perform a risk-adapted monitoring according to its monitoring SOP. The source data/documents as well as the investigator site file are accessible to monitors and questions are answered during monitoring. The extent and nature of monitoring activities are described in a study specific monitoring plan written by the Sponsor.

12.4 Audits and Inspections

The SPOG routinely audits its member institutions. The study can be audited in the course of such audits. No additional audits are planned specifically for this study. The Sponsor and the authorities have the right to conduct audits and inspections.
The study documentation and the source data/documents are accessible to auditors/inspectors, and questions are answered during inspections. All involved parties must keep the participant data strictly confidential.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring (see 12.3), audits and inspections (see 12.4).
The protocol is not confidential, it is intended to be made publicly available (see 13).
The Sponsor has no access to non-coded patient data.
The members of the Study Committee will have access to the anonymized dataset, the statistical code, and other relevant information during and after the study.
A set of fully anonymized essential data can be made publicly available after publication of the main results. In the resulting publications, identification of participants will be impossible.

13. PUBLICATION AND DISSEMINATION POLICY

The main results of this study will be communicated to participants, their parent, and the involved healthcare professionals by a letter in lay language.
The detailed results will be submitted for publication in peer-reviewed journals. The reporting requirements of the CONSORT statement, including its extension for reporting non-inferiority trials, will be fulfilled [37,48]. The current version of the ICMMJE recommendations [49] is applicable regarding authorship eligibility. The use of professional writers is not intended.
The protocol is not confidential, it is intended to make it publicly available (see 12.5). A set of fully

anonymized essential data can be made publicly available after publication of the main results. The Study Committee decides on all further aspects of publication.

14. FUNDING AND SUPPORT

Funding has been granted by Krebsliga Schweiz (KFS-3645-02-2015). This funding has no influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript. Further support may be searched only from institutions that will have no influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript.

15. INSURANCE

Insurance will be provided by the Sponsor in compliance with Swiss law. A copy of the certificate is filed in each study site file and the study master file.

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17. APPENDICES

A. List of Study Sites and Local Principal Investigators
An updated List of Study Sites and Local Principal Investigators is available from the SPOG Office (see 1.1)

B. Model Patient/Parent Information and Informed Consent forms

Model versions of the following forms, all in German and French versions, are available from the SPOG Office (see 1.1):

- Patient Information, patients 11 to 13 years old
- Patient information, patients ≥14 years old
- Parents' information
- Informed Consent

C. Case Report Forms
A set of paper CRFs is available from the SPOG Office (see 1.1)

D. Amendment 1
See pages 36 to 37 for an overview of Protocol changes introduced in Amendment 1, from Protocol version 1.0 of March 07, 2016, to version 1.1 of November 23, 2016.

Appendix D: Protocol changes introduced in Amendment 1,

from Protocol version 1.0 of March 07, 2016, to version 1.1 of November 23, 2016

~~Deleted items~~ are marked as deleted, **new items** are marked in bold.

1. Correction of typos

Minor typos have been corrected throughout all documents.

2. Formal updates

a) Change, address SPOG (protocol 1.1)
"Effingerstrasse ~~40~~ **33"**

b) Change, mail-address Katrin Scheinemann (protocol p.1)
"katrin.scheinemann@~~luks~~**ukbb**.ch"

c) Change, mail address Karin Zimmermann (protocol p.1)
"karin.zimmermann@~~insel~~**unibas**.ch

d) Change, mail address Philipp Agyeman (protocol p.1)
"philipp.agyeman@~~gmail.com~~**insel.ch**

e) Change, version number and date (throughout protocol)
"~~1.0 / March 07, 2016~~ **1.1 / November 23, 2016"**

f) New, SNCTP number (protocol p.2, Synopsis, 2.1)
"**www.kofam.ch: SNCTP000001776"**

3. Additional members in Study Committee

Reason: Include PIs of initial set of recruiting Swiss study sites

a) New, PI of Geneva, Marc Ansari (protocol p.1)
"**Marc Ansari, MD marc.ansari@hcuge.ch Ped. Oncology**"

b) New, PI of Lucerne, Johannes Rischewski (protocol p.1)
"**Johannes Rischewski, MD johannes.rischewski@luks.ch Ped. Oncology**"

4. Clarifications in the protocol

a) Adjust definition of "slightly elevated temperature", and thus possible FN, to situations with continued use of antipyretics (protocol 5.1.3)
"… at least slightly elevated temperature (≥38.0°C) … . **In rare exceptions, to be discussed individually with the Study Chair / Study Vice Chair, this limit can be further lowered to 37.5°C in patients repeatedly receiving antipyretics despite neutropenia, a practice strongly discouraged by this protocol."**

b) Clarify duration of FN episodes, considering restart of i.v. chemotherapy, adjust corresponding duration of outcome tracking (protocol 5.1.5)
"… same FN episode. **Start of intravenous chemotherapy immediately ends an FN episode, overruling the preceding definition**. Correspondingly, all outcomes are tracked … therapy for FN**, as long as neutropenia persists and intravenous chemotherapy has not been started**."

c) Adjust to clinical reality: time delay allowed since last CBC used for decision on potential FN_{Clin} (protocol 9.2.2)
"(last CBC >48 **[72 in unequivocal situations]** hours old, or…"

d) Clarification of duties in processing SAE reports and which SAEs need to be reported to CECs (protocol 10.2)
"The Study Chair / Study Vice Chair **checks SAE reports for medical consistency and for completeness, sends the respective queries to study sites where needed, and** performs a plausibility check …. ~~In parallel~~ **If a relatedness of the SAE to the intervention studied cannot be excluded** the Sponsor informs… . **If Sponsor and Study Chair / Study Vice Chair cannot resolve discrepancies**

regarding the question of such relatedness, an external expert is asked for advice."

e) Clarification of timelines for reporting deaths in ongoing SAEs (protocol 10.2)

"Deaths during ongoing SAEs have to be reported within the same timelines specified above (24 hours or 7 days, respectively)"

5. Allow participation of patients in/after myeloablative therapy followed by autologous hematopoietic stem cell transplantation (synopsis, protocol 7.2)

Reason: New consensus among transplanting sites reached that study is feasible in autologous transplant setting

in "Inclusion criteria"

"~~Myelosuppressive (not myeloablative only) c~~**C**hemotherapy treatment because of any malignancy planned for at least 2 further months at time of recruitment **for myelosuppressive therapy, or at least 1 cycle of myeloablative chemotherapy followed by autologous hematopoietic stem cell transplantation**"

in "Exclusion criteria"

"Past ~~autologous or~~ allogeneic hematopoietic stem cell transplantation"

6. Clarification of end of study criteria

Reason: Addition of mandatory criterion, and completing the list of criteria in protocol (protocol 7.5)

"7.5 Criteria for withdrawal / discontinuation **/ end of study** of patients

Patients are withdrawn from the study in case of withdrawal of informed consent, **and when study participation is not in the best interest of the patient any more, including** relevant non-compliance, as judged by the study site **or the study center**. **The study ends regularly** when ~~they~~ **patients** have reached the age of 20 years, **at the end of the study as such, at the first day of** ~~or when they receive~~ myeloablative chemotherapy **before allogeneic hematopoietic stem cell transplantation** ~~(chemotherapy intensity 4, see 5.1.6)~~, **21 days after the last dose of chemotherapy, or at the day of death from any cause**.