Continuous monitoring of health data with a wearable device in pediatric patients undergoing chemotherapy for cancer – a feasibility pilot study

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A acc. to ordinance HRO Art.7
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PROTOCOL SIGNATURE FORM

Study Title	Continuous monitoring of health data with a wearable device in pediatric patients undergoing chemotherapy for cancer – a feasibility pilot study

The project leader has approved the protocol version ***[0.7 (dated 29.10.2019)]***, and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles of Good Clinical Practice.

Project leader and Sponsor:

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Name: Eva Brack

Date: 29.10.2019 Signature: 

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
WD	*Wearable device*

1 BACKGROUND AND PROJECT RATIONALE

Pediatric patients with cancer and chemotherapy-induced neutropenia are at great risk to develop severe and potentially life threatening infections. Initially, fever is often the only clinical detectable sign of such an infection. Therefore, fever in neutropenia is treated as an emergency, including hospitalization, start of intravenous empirical broad-spectrum antibiotics and close monitoring.
Several clinical decision rules have been established to distinguish between severe and less severe infections, based on the patient's history, clinical appearance and laboratory signs [4, 5], but with the exception of fever, vital signs are hardly explored. Delay of diagnosis and treatment can result in increased mortality [6], more intensive treatment [7] and more adverse events [8]. Time from hospital admission to antibiotics has been shown to influence clinical outcomes [8].
Wearable devices (WD) are already frequently used by athletes to monitor their activities and vital signs. Those devices are becoming smaller, more powerful and sophisticated and allow continuous recording of health data nearly everywhere and under any condition. Also in medical settings, WD are increasingly used for continuous measurements of patients' health data [9, 10]. Non-invasive on-skin wearable monitoring devices offer a broad set of health data that is recorded continuously [11].
It is hypothesized that continuous health data monitoring will provide more detailed information, and an more exact representation of the patient's health status than discrete measurements. Specifically it has been shown, that infections trigger changes of vital-signs very early in their course. For example heart-rate variability has been identified to change before clinical symptoms are detectable in neonates with sepsis [12] and in adults who underwent bone marrow transplant [13, 14]. Using a WD therefore opens the possibility to identify health data patterns that might be used as an additional diagnostic tool or a tool predicting imminent fever or infection in the near future. This may lead to earlier diagnosis and shorter time to antibiotics in patients at high risk for severe infection and the distinction from patients at lower risk.

1.1 Clinical Evidence to Date

Continuous monitoring with wrist-worn WDs has been shown to be possible for heart rate (Fitbit Charge HR©) [15] and physical activity (GENEActiv accelerometer) [16, 17] in healthy children. Several studies have assessed physical activity in pediatric patients undergoing chemotherapy with WDs worn on the ankle (StepWatch 3™ Activity Monitor) [18], waist (MTI Actigraph accelerometer) [19]; (Actical activity monitor) [20] or clothes (FitBit®) [21]. But no study has proven feasibility of continuous monitoring of other health data or vital signs with any WD in pediatric patients undergoing chemotherapy for cancer (search in PubMed, using (Accelerometer OR Wearable Electronic Devices/ OR wearable OR sensor OR tracker*) AND (child OR children OR pediatric OR paediatric) AND (cancer/ OR cancer OR oncology), performed on June 20, 2019). It is not known if children tolerate a WD worn on the upper arm or thigh and if data quality sustains. Neither is it known if parents and patients can and are willing to handle a device in outpatient settings.

We know of a currently ongoing pilot study in pediatric inpatients aged 4 to 16 years with perforated appendicitis, osteomyelitis or septic arthritis, investigating the feasibility of continuous vital sings assessment with the Everion® at the University of Basel Children's Hospital (BASEC ID 2018-01926). In contrast to the present study, the Basel study excludes outpatients and patients below 4 years of age. Besides, the setting for children and adolescents undergoing chemotherapy for cancer is not comparable to patients receiving antibiotics for infections.

Additionally Everion® is currently investigated as one of five devices in an ongoing study trying to assess changes in physiological signals before and during seizures in children with epilepsy (NCT03745118).

2 PROJECT OBJECTIVES AND DESIGN

2.1 Primary objective

To assess the feasibility of continuous monitoring of heart rate in pediatric patients undergoing chemotherapy for cancer using the WD.

2.2 Secondary objectives

Secondary objectives are related to:

A. Further feasibility aspects

B. Comparison of continuously recorded data with results of discrete measurements performed for clinical routine care

C. Exploration for specific patterns in continuously recorded data before and during episodes of fever and infection

2.3 Choice of WD

The WD investigated in this study is the Everion® by Biovotion, Zurich, Switzerland. To continuously monitor health data in children, a light and easy wearable device is needed, that does not hamper the child in any way during daily activities. The handling should be easy for the patients and/or parents to minimize the additional burden during the intensive treatment phases of chemotherapy. The Everion® is light (approximately 40g), without buttons and cables, and can be worn with an elastic band. Once the band is put on, the patient cannot tighten the band any further, as the size can only be adjusted by choosing the appropriate band size. This is more secure than an adjustable band for young children. As it is not known yet how to interpret the recorded data, it is necessary that the patients, parents and treating personnel do not have direct access to the data, as there is a risk for misinterpretation. In contrast to other WD, as smart-watches, the recorded data is not displayed on this WD. The Everion® is designed to measure with medical grade quality and provides a quality indicator for all calculated signals. It is CE-certified (CE 0123), medical device class IIa and FDA 510(k) exempt listed. Regulatory information: CE0123 ; MD Directive 93/42/EEC; RoHS Ro2011/65EU; Radioequipment Directive 2014/53/EU; Low Voltage Directive 2006/95/EC; WEE 2012/19/EU; EMC 2014/30 EU. One WD will be used for several patients, the WD is disinfected between different patients. For each patient a new elastic band will be used.

2.4 Signals and scores collected

Everion® generates signals as vital signs or scores at a frequency of one per second. For this study aggregates will be used. Aggregates are filtered or averaged versions of signals and will be calculated every minute. Aggregates are calculated as quality-weighted average considering all signals whose quality is >50 and then weights each signal by the quality-30. The associated quality score is the average of all quality values >50, if more than 10% of quality values are >50, else it is the average of all quality values <50. For signals without quality scores aggregates are calculated as median value for all signals in the aggregation period of three minutes.

Description of Aggregates	unit	range	ID	Quality Score	name	ID
Signals comparable with discrete measurements						
S.1 HEART RATE	bpm	30-240	6	Q.1	HEART RATE QUALITY	68
S.2 OXYGEN SATURATION	%	60-100	7	Q.2	OXYGEN SATURATION QUALITY	69
S.3 RESPIRATION RATE	bps	2-60	12	Q.3	RESPIRATION RATE QUALITY	75
S.4 CTEMP (Core temperature)	°C	21-46	15	Q.4	CTEMP QUALITY	76
S.5 TEMPERATURE OBJECT (skin temperature)	°C	-10-40	118	-	-	-
Signals for general performance						
S.6 HEART RATE VARIABILITY	ms	2-140	11	Q.6	HEART RATE VARIABILITY QUALITY	74
S.7 PERFUSION INDEX	-	0-5	8	Q.7	PERFUSION INDEX QUALITY	133
S.8 HEALTH SCORE	-	0-100	22	-	-	-
S.9 GSR (Galvanic skin response)	kOhm	0-5	21	-	-	-

Quality Scores
Q.1 to Q.4 and Q.6: Quality scores for Signals S.1 to S.4 and S.6 [0 to 100; ≥50 indicates at least acceptable quality]
Q.7 Quality score for Signal S.7, perfusion of the skin [0 to 5.2; Higher values indicate better perfusion leading to better overall quality measurements; no limit defined for acceptable quality]

2.4 Primary and secondary endpoints

The primary outcome is defined as at least acceptable (≥50) quality score Q.1 (see 2.3) of heart rate S.1 during a cumulative duration of ≥18/24h per day (midnight to midnight), during ≥7 consecutive days within the 14 days of study duration (binary outcome, measured once).

A. Secondary feasibility-related outcomes:
A1) At least acceptable quality scores (Q.2 to Q.4 and Q.6/7) of further signals (S.2 to S.4 and S.6/7 (see 2.3) during a cumulative duration of ≥18/24h per day (midnight to midnight), during ≥7 consecutive days within the 14 days of study duration (binary outcomes, measured once).
A2) Cumulative length of time with at least acceptable quality scores Q.1 to Q.4 and Q.6/7 (see 2.3) per study day (continuous outcomes, measured daily).
A4) Primary outcome and secondary outcomes A1 and A2 by skin type according to the Fitzpatrick scale [22] (Appendix 1).
A4) Primary outcome and secondary outcomes A1 and A2 by activity reported by parents and patients if applicable.
A5) Proportion of patients and parents indicating that continuous monitoring with the WD is acceptable per day and per entire study duration (binary outcome, measured daily plus once).
A6) Reasons not to wear the device as reported by parents and by patients if applicable (categorical outcome, measured daily).
A7) Side effects reported by parents and patients, if applicable (categorical outcome, measured daily)
A8) Effort (cumulative number and duration of contacts) per study day for the investigators (continuous outcomes, measured daily).

B) Secondary comparison-related outcomes:
B1) Difference between discrete measurements performed for clinical routine cares of heart rate and the mean of continuously measured signal S.1 (heart rate) within +/-10min at times of the discrete measurement (continuous outcomes, measured potentially multiple times).
B2) Like B1, for percutaneously measured blood oxygenation and signal S.2 (Oxygen Saturation).
B3) Like B1, for respiration rate and signal S.3 (respiration rate).
B4) Like B1, for ear temperature and signal S.4 (core temperature).
B5) Like B1, for ear temperature and signal S.5 (skin temperature).

C) Secondary outcomes for the exploration of specific patterns
C1) Exploration of potential changes in or specific patterns of the measured signals S.1 to S.9 and quality scores Q.1 to Q.6, within 48 hours before and after clinical diagnosis of fever (ear temperature of ≥39.0°C, or ≥38.5°C if fever is declared for clinical reasons) with or without neutropenia and microbiologically or clinically defined infections, if applicable.
C2) Like C1) for further signals collected with the WD.

2.5 Project design

This is an investigator-initiated, single-center observational pilot study on the feasibility of continuous monitoring of health data with a WD in pediatric patients undergoing chemotherapy of cancer. For patients with cancer, the risk for severe infections is the highest during phases with chemotherapy induced neutropenia. Neutropenia normally last about 10 to 14 days. To detect severe infections earlier, this expected time period with neutropenia, is the period, in which continuous monitoring of health data does make most sense. Therefore, in this study the WD will be studied in the patients for 14 days.
A total of 20 patients will be included, including at least 4 patients <6 years. As this is a feasibility study, a formal sample size calculation has not been performed. However, this sample size allows to assess the primary outcome with clinically meaningful precision and to roughly assess the primary outcome in the group of patients <6 years of age.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

Inclusion criteria:

- Chemotherapy treatment because of any malignancy, expected to last ≥1 month at time of recruitment for myelosuppressive therapy; or at least one cycle of myeloablative therapy requiring autologous hematopoietic stem cell transplantation.
- Age from 1 month to 17.99 years at time of recruitment
- Written informed consent from patients and/or parents

Exclusion criteria:

- Local skin diseases prohibiting wearing of the WD.
- Denied written informed consent from patients and/or parents

3.2 Recruitment, screening and informed consent procedure

This study will be conducted at the Inselspital, Bern University Hospital. Recruitment will take place at the Department of Pediatrics, in the Division of Pediatric Hematology/Oncology.
Patients will be screened for eligibility and recruited by a study investigator or treating physician.
No specific screening procedures except verifying inclusion/exclusion criteria are needed.
Patients will be assessed during a routine outpatient visit, or during hospitalization. Patient recruitment will stop when the aimed number of twenty patients is reached.
No payment or compensation will be given to study patients or their parents.

The investigators will explain to the parents/legal representative and the patient if applicable, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. The parents/legal representative and the patient if applicable, 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 parents/legal representative and the patient if applicable, must be informed that the medical records may be examined by authorized individuals other than their treating physician.
The parents/legal representative and the patient if applicable, will be provided a patient information sheet and a consent form describing the study and providing sufficient information for parents and patients to make an informed decision about their participation in the study. Sufficient time will be given to make the decision.
The formal consent of the parents/legal representative and the patient if applicable, 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.
The parents/legal representative and the patient if applicable, 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) at the same time as the patient sign, and it will be retained as part of the study records.

3.3 Study procedures

Study Periods	Screening	Study visit	Study period	Follow-up
Time (day)	0, 1 or before	0 or 1	1 -14	15 to 17
In- /Exclusion Criteria	x			
Patient Information and Informed Consent	x			
Further patient characteristics	x			
WD distribution		x		
WD instructions		x	x	
Wearing the WD		x	x	
Primary outcome		x	x	
Secondary outcomes		x	x	x
Side effects		x	x	x

3.1.1 Study visit

The study visit will be done during a routine outpatient visit, or during hospitalization. One of the study investigators will distribute the WD, the charger, and if needed the mobile phone to the parents or patient. Parents and/or patients, with no suitable mobile phone, will be provided with a phone for the study time. This phone will not be usable for other purposes than data transfer. Basic characteristics as age, height, weight, thigh and arm circumference and skin type will be assessed at the study visit.
The WD is fitted using body size-appropriate elastic bands and the fitting is controlled by the investigator. Parents and patients if applicable, will be instructed in the handling and charging of the WD. For instructions, the pictures and descriptions provided by the manufacturer on the website, in the “instructions for use” handbook and the information in the study information form will be used. Instruction on how to install the mobile phone app for data transfer will be provided (see 7.2). The WD will be put on the upper arm or, if anatomically reasonable, on the upper leg.

3.1.2 Study period

There will be no additional examinations or procedures performed for this study, specifically no additional discrete measurements of vital signs will be undertaken unless the clinically indicated measurements. Daily activities and temperature measurements if taken during outpatient stay will be recorded on case report forms (CRF) by parents and/or by patients. Questionnaires will be used for the assessment of WD acceptance, side effects and reasons not to wear the device. Parents, patients and members of the treating staff will not be able to access the continuously measured data, in order to avoid any influence on clinical decision making due to these data.

During the measurement period of 14 days no extra visits are planned. During the whole study period, one of the investigators will do a daily data-check, to see if data is recorded properly or not. If no data is recorded or if there are signs for reduced data quality, the parents and/or patients will be contacted by phone. Possible reasons for non-recording or reduced data quality

will be discussed on the phone and instructions will be given to parents and/or patients. During hospital visits calls may be replaced by on ward visits.

Parents and/or patients can contact the study site by phone any time by calling the pediatric oncology ward (24h emergency number) or outpatient ward and ask for assistance with the WD. Investigators are allowed to additionally check data recording, when contacted by parents or patients. Date, number, duration and reason of phone contacts and visits will be noted.

During the study period, parents and/or patients will be in charge for battery charging (approx.2 hours each day) and data upload via mobile phone app. Parents and/or patients will fill out a CRF daily and note time of charging, connection to the mobile phone, reasons for not wearing the WD, any side effects, activities and temperature measurements, if applicable.

During hospitalization treating staff will perform discrete measurements as clinically indicated and note them in the patient chart. Parents and/or patients will continue to fill out the CRF daily. The charts will be assessed by the investigators to match the recorded data with the data from the WD.
The study period ends regularly for each patient after the planned period of 14 days, in case of intensive care unit admission or at the day of death from any cause, unrelated to the study.

3.1.3 Follow-up

Follow-up period covers 24hours after the end of the study period. The respective follow-up interview by phone or if applicable during a routine hospital visit will take place 1 to 3 days after the end of the study period.

3.4 Withdrawal and discontinuation

Non-compliance, mainly not wearing or charging the WD, will not lead to exclusion from the study, as this is directly linked to the primary outcome.

In case of withdrawal of informed consent no data will be collected beyond the date of withdrawal except for tracking of side effects for 24 hours after the last time the WD has been worn. The information collected until this date will be used for analysis. This information will be fully anonymized after analysis.

4 STATISTICS AND METHODOLOGY

4.1 Statistical analysis plan

For the primary outcome the proportion of patients and its exact 95% CI will be calculated. Feasibility of continuous monitoring of heart rate in pediatric patients under chemotherapy will be claimed if 15 of 20 patients (75%) fulfil the primary outcome.
For all outcomes, descriptive statistics using standard methods, including graphical methods, will be performed and exact 95% CI for proportions and estimates, where applicable, will be calculated.
For exploratory analyses different methods adapted to data types will be used.
The analyzed dataset contains all included patients. The current version of the R software [23] will be used for analysis.

4.2 Handling of missing data

There will be no imputation for missing data. No replacement of drop-outs is done, because the target assessed primary outcome will include drop-outs.

4.3 Planned Timetable

There are at least 20 patients under chemotherapy in the study site at any given time point and about 40 patients with newly diagnosed cancer per year. We expect a participation rate of about 75% and thus a study duration of three to four months. We will use ten to twenty in parallel usable WDs.

2019, June	Submission to pediatric IRB Bern
2019, August	Submission to CEC
2019, December	Recruitment of first patient
2020, March	Last patient out
2020, May	Data closure, clean data
2020, July	Data analyzed
2020, October	Manuscript with main results submitted

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the collection of health-related personal data using the WD, and which:

- requires inpatient treatment not envisaged in the treatment protocol or extends a current hospital stay;
- results in permanent or significant incapacity or disability; or
- is life-threatening or results in death.

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21 [1]. The project leader will submit a report to the responsible Ethics Committee which evaluates the relationship between the event reported and the methods of collecting health related personal data within the project, and propose how to proceed with the project.

During this study the included patients are undergoing clinical procedures as per standard of care for their cancer diagnosis, which will cause side events unrelated to the study procedures and will not be reported.

5.4 Procedure for investigations involving radiation sources

No radioactive sources are used in this research project.

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project termination, the Ethics Committee is notified within 90 days. All health-related data are anonymized upon termination of data analysis. Records and documents pertaining the conduct of this study, including source documents, CRFs and consent forms will be retained for 10 years.

5.7 Insurance

In the event of project-related damage or injuries, the liability of the Inselspital Bern provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

The research project will be carried out in accordance to the protocol and the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) and the ISO Norm 14155, the Swiss Law and Swiss regulatory authority's requirements. The CEC will receive annual safety reports and will be informed about study stop/end in agreement with local requirements.
The study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

6.2 Risk-Benefit Assessment

For the participants this study has minimal risks:

- Pressure: If the WD is attached too tight, this can result in pressure and stasis injuries.
- Skin reactions: Allergic reactions to the materials used, skin reactions because of moisture or dirt between the skin and the device, or skin reactions to friction of the device against the skin may occur.
- Child distress: Young children may not understand the purpose of this study and of wearing the WD. Therefore, they could show symptoms of distress as persisting crying and resistance against attachment of the WD.

Training and information of parents and of patients if applicable, will minimize these risks. The WD is fitted using body size-appropriate elastic bands. After fitting, the size of the band cannot

by tightened any further by the patient. Regular cleaning of the skin underneath the device and of the device itself will be instructed.

In this study, there are no direct benefits for the patients. The knowledge gained from this study, and potential future studies building upon the results of this study may help to provide better care for future pediatric patients, including pediatric patients undergoing chemotherapy for cancer.

6.3 Rationale for the inclusion of vulnerable participants

Health data in children and adolescents is known to differ in many core characteristics from health data in adults and can therefore not be extrapolated from adults. To assess feasibility of continuous monitoring of health data in pediatric patients specifically, children and adolescent need to be studied themselves, despite them being especially vulnerable study participants.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions. All staff involved are trained in project related procedures and all important aspects.

7.2 Data recording and source data

Baseline patient data and information on disease and treatment, where relevant, will be extracted from electronic medical records. Investigators and staff of the study site delegated to complete CRFs will record study-related information on patients.
Data recorded by the WD will be transferred to the mobile phone via Bluetooth and then uploaded in a pseudonymized fashion to a web-based password-protected dashboard. The WD cannot be linked with other devices and recorded data cannot be read by third parties, nor by the parents and patients. Biovotion is ISO 13485 certified [24] and guarantees data security in compliance with the EU General Data Protection Regulation. Biovotion will provide an application programming interface, so that the investigators can download the data themselves. Access and retrieval of the data from the dashboard is secured by a password. All data are transferred and stored using encryption (TLS, https).

Source documents include the patients' charts (electronic as well as paper), which are stored at the site-specific usual location for charts. Data recorded by the WD will be downloaded by the investigators and stored electronically in a SharePoint Databased provided by the CTU Bern. This database will be used as source document for the WD data, as the web-based dashboard is not convenient for long term data storage.
If parents and patients if applicable consent, collected data will be published in anonymized form. Study-specific documents (Informed Consent Forms, screening form, patient identification list and relevant correspondence) are filed in the Investigator Site File. The Investigator Site File is stored in a closed location of the "study center".

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized staff who require the data to fulfill their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique patient number (ID). The patient identification list will be stored by the project leader.

Confidentiality of the patients will be maintained by assigning a unique patient number (ID), keeping identifiers separate from the data and storing data in a locked file with password access and secure computer database in line with Swiss legal requirements. Scientific reports generated from the study will not contain information that would identify the participating children. Biovotion Zurich signed a data processing agreement and agrees not to try to re-identify the pseudonymized data and to maintain confidentiality about all information.

7.4 Retention and destruction of study data and biological material

Source documents and documents pertaining to the conduct of this study, including CRFs, and consent forms, are archived for a minimum of 10 years after the completion or premature termination of the study.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

Funding for this study will be searched by grant applications to the “Batzebär” foundation and, for backup, to the “Berner Stiftung für Krebskranke Kinder und Jugendliche”. These institutions will have no influence on the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The main results of this study will be communicated to the parents and the patients if applicable, and the treating staff involved in a letter written in lay language.
The detailed study results will be submitted for publication in peer-reviewed journals. The current version of the ICMMJE recommendations regarding authorship eligibility is applicable.
The use of professional writers is not planned.
The protocol is not confidential; it is intended to be made publicly available.
There is no conflict of interest for the Sponsor-Investigator and for all study investigators.

9 REFERENCES

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Appendix 1: Fitzpatrick Scale

The Fitzpatrick skin type classification denotes six different skin types [22, 25]. The scale is based on a questionnaire related to an individual's genetic constitution, reaction to sun exposure and tanning habits. The response to all questions are added to get the final score (all tables from: Sachdeva S. Fitzpatrick skin typing: Applications in dermatology. Indian J Dermatol Venereol Leprol 2009 [25])

Table A1: Genetic disposition, total score 0-16

Score	0	1	2	3	4
What is the Colour of your eyes?	Light blue, grey, or green	Blue, grey, or green	Blue	Dark brown	Brownish black
What is the natural colour of your eyes?	Sandy red	Blond	Chestnut/dark blond	Dark brown	Black
What is the colour of your skin in the nonexposed areas?	Reddish	Very pale	Pale with beige tint	Light brown	Dark brown
Do you have freckles in the nonexposed areas?	Many	Several	Few	Incidental	None

Table A2: Reaction to sun exposure, total score 0-16

Score	0	1	2	3	4
What happens when you stay in sun too long?	Painful redness, blistering, peeling	Blistering followed by peeling	Burns sometimes followed by peeling	Rare burns	Never had burns
To what degree do you turn brown?	Hardly or not at all	Light color tan	Reasonable tan	Tan very easy	Turn dark brown quickly
Do you turn brown within several hours after sun exposure?	Never	Seldom	Sometimes	Often	Always
How does your face react to the sun?	Very sensitive	Sensitive	Normal	Very resistant	Never had a problem

Table A3: Tanning habits, total score 0-8

Score	0	1	2	3	4
When did you last expose the body to sun (or artificial sunlamp/tanning cream)?	More than 3 months ago	2–3 months ago	1–2 months ago	Less than a month ago	Less than 2 weeks ago
Did you expose the area to be treated to the sun?	Never	Hardly ever	Sometimes	Often	Always

Table A4: Total score of table A1 to A3 corresponding to Fitzpatrick skin Type

Skin type score	Fitzpatrick skin type
0-7	I
8-16	II
17-25	III
25-30	IV
over 30	V–VI