Statistical Analysis Plan

Study Information:

Sponsor Study Code:	CLIN-0012
Study Title:	A Single Center, Pilot Clinical Investigation of Surgical Bleeding in Burn Patients, and Chronically Transfused Patients with Haematologic Malignancies, who are Transfused with Hypoxic Red Blood Cells Manufactured with Hemanext ONE system
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Table of Content

Acronyms & Abbreviations	
AABB	Association for the Advancement of Blood and Biotherapies
ADE	Adverse Device Event
AE	Adverse Event
ABG	Assessment of Arterial Blood
ATC	Anatomical Therapeutic Chemical [classification system]
BEST	Biomedical Excellence for Safer Transfusion
BMI	Body mass index
BSA	Body Surface Area
BV	Blood Volume
CIP	Clinical investigation plan
CRF	Case report form
DDP	Data display plan
EU	European Union
FAS	Full analysis set
HGB	Hemoglobin
ICH	International Council on Harmonization
IMP	Investigational medicinal product
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
PPAS	Per-protocol analysis set
RBC	Red blood cell
SAP	Statistical analysis plan
SADE	Device deficiency with Serious Adverse Device Effect
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TBSA	Total Body Surface Area
USADE	Unanticipated / Unexpected Serious Adverse Device Effect
VS	Vital Signs
WHO	World Health Organisation

1 Acronyms and Abbreviations used in the Document

2 Introduction

The Statistical Analysis Plan (SAP) is a complementary document to the Clinical Study Protocol and includes a more technical and detailed elaboration of the principal features of the proposed statistical analysis and presentations, and the way in which anticipated analysis problems will be handled.

If the SAP suggests changes to the principal features stated in the protocol, these should also be documented in a protocol amendment. Otherwise, it will suffice to record the changes in the SAP.

3 Study Objectives

3.1 Primary Objective

A. For both patient groups

To assess the safety and tolerance of Hypoxic RBCs up to 24 hours following the transfusion initiation and overall, up to 7 days (+/- 1 day) after the transfusion episode (single transfusion course).

3.2 Secondary Objectives

B. For both patient groups

1. Assessment of pre and post transfusion hemoglobin levels
2. Assessment of hemoglobin level before the following transfusion, if applicable
3. Assessment of AEs occurrence:
    i. Up to 7 days (+/- 1 day) post transfusion (including but not limited to infection, deep vein thrombosis, acute respiratory distress syndrome, transfusion-related acute lung injury, transfusion associated circulatory overload, anaphylactic shock, acute haemolytic transfusion reaction).
    ii. Up to the subsequent transfusion episode or up to 28 days (+/- 1 day) after the initial transfusion, whichever comes first.
    iii. From enrolment, up to their subsequent transfusion or 28 days (+/- 1 day) post transfusion, whichever comes first, through the assessment of patient's diary
4. Assessment of the Vital Signs (VS) during and up to 15 minutes after the transfusion

C. For burn patient group only:

1. Assessment of arterial blood gases:
    i. pre-operative
    ii. intra-operative
    iii. post operative

3.3 Clinical investigation outcomes

3.3.1 Primary outcome

Number of participants who experienced an adverse event (all types/grades) from transfusion up to 24 hours and 7 days (+/- 1 day) post transfusion.

3.4 Secondary Outcomes:

1. Evaluation of blood pH, pO2, pCO2, HCO3 and base (excess) before, during and after the transfusion (Burn patients group only).

2. Hemoglobin level before the following transfusion
3. Frequency of all AEs, including transfusion related AEs up to 7 days (+/- 1) post-transfusion
4. AEs up to 28 days after the initial transfusion, or up to subsequent transfusion episode, whichever comes first.
5. Frequency of all AEs, from enrollment, up to 7 days (+/- 1 day) post transfusion, through the assessment patient's diary, when applicable.
6. Vital signs over the course of the transfusion and up to 15 minutes post-transfusion.

4 Study Design

This is a single center clinical trial of surgical bleeding in burn patients, and chronically transfused patients with haematologic malignancies. Patients are transfused with hypoxic red blood cells manufactured with Hemanext ONE system". The patient groups are burn patients and chronically transfused patients with haematologic malignancies. Patients need to be adults ≥ 18. There will be no randomization of Patient s, no blinding, and no comparator.

A first cohort of 5 patients – solely from the hematological malignancies (chronically transfused) group - will be enrolled, transfused and followed-up until their subsequent transfusion or 28 days (+/- 1 day) post-transfusion, whichever comes first. All safety related data from this initial cohort of 5 patients will be reviewed and assessed by the clinical investigation Data Monitoring Committee (DMC). Upon favourable opinion from the clinical investigation DMC, the enrolment of the remaining patients (both groups) will resume until completion.

Each patient is expected to attend 5 visits:

1. Visit 1 (Screening): Determine eligibility and obtain baseline data, physical examination, and safety assessments.
2. Visit 2 (Transfusion Day):
    a. Pre-Transfusion: eligibility, hemoglobin, and safety assessments
    b. Transfusion: transfusion, safety assessments, and device integrity
    c. Post-Transfusion: safety assessments, hemoglobin, and device integrity
3. Visit 3 - Follow-Up (24 hours post-transfusion): safety assessments and device integrity
4. Visit 4 - Follow-Up (7 days (+/- 1) post-transfusion): safety assessments, and device integrity
5. Visit 5- Final Follow-Up (28 days (+/- 1 day)): hemoglobin and physical examination

A complete study flow chart for Hematogical Malignancies Group is presented in Appendix A: and a complete study flow chart for Burn patients Group in Appendix B: .

5 Study Population

The study population consist of two sperate groups of adult patients (≥ 18) male and female:

1. Acute burn patients, hospitalized with a Total Body Surface Area (TBSA%) burn ≥ 10% and ≤50% expected to require > 2 unit of red blood cells in a single transfusion event.
2. Hematologic malignancies patients identified by a Transfusion hemoglobin trigger of less than 9 g/dL with a documented diagnosis of leukemia, myelomatosis or myelodysplastic syndromes (MDS) and requiring chronic transfusions. Patients expected to require > 2 units of red blood cells in a single transfusion event.

5.1 Sample Size

A total of twenty patients - 10 burn patients and 10 patients with haematological malignancies will be enrolled in the study. Twenty patients will be sufficient to assess preliminary safety of O2/CO2 reduced RBCs, as the rate of transfusion related adverse events is usually low and if unexpected adverse events (any type or grade) should occur, this will be identified. There are no statistical criteria for choosing twenty patients.

6 Assessments

A schedule of assessments can be found in Appendix A: for Hematological malignancies patient group and Appendix B: for Burn patients Group.

6.1 Safety Assessments

6.1.1 Assessment of Adverse Event and Adverse Device Effect

Patients will be monitored for Adverse Events (AE) and Adverse Device Effects (ADE) throughout the entirety of their participation in the clinical investigation from Visit 0 (Screening) to Visit 5 (Follow-Up 2). AEs and ADEs will be categorized as described in Section 6.1.2 to Section 6.1.12. Investigators will monitor patients directly for AEs and ADEs during their transfusion visit. In addition, patients will be contacted by phone at Visit 3 (24 hours post transfusion) and at Visit 4 (7 days (+/- 1)) after their transfusion visit to record any AEs and AEDs they have experienced since the transfusion Visit 2 (transfusion visit).

6.1.2 Adverse events

All AEs will be recorded. That includes any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in Patients, users, or other persons even if not related to the medical device.

6.1.3 Serious Adverse Event (SAE)

Any adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the patient that resulted in any of the following:

   I. life-threatening illness or injury,

   II. permanent impairment of a body structure or a body function,

   III. hospitalisation or prolongation of patient hospitalisation,

   IV. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

   V. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the clinical investigation plan (CIP), without a serious deterioration of the health status of the patient, is not considered an SAE

6.1.4 Causal Relationship of SAE

A causal relationship towards the medical device or the procedure of the investigation:

- **Not related**: The relationship to the device or procedures can be excluded.
- **Possible**: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable**: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship**: The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

6.1.5 Adverse Device Effect (ADE)

AE possibly, probably, or causally related to the use of an investigational device or procedures.

6.1.6 Serious Adverse Device Effect (SADE)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a SAE

6.1.7 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer. Device deficiency data will be collected by the blood banks and the clinic staff.

6.1.8 Malfunction

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

6.1.9 Unanticipated Serious Adverse Device Effect

SADE which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

6.1.10 Device deficiency with Serious Adverse Device Effect (SADE)

Any device deficiency that might have led to a serious AE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

6.1.11 Serious Health Threat:

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in patient s, users, or other persons, and that requires prompt remedial action for other patients, users or other persons Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

6.1.12 Unanticipated / Unexpected Serious Adverse Device Effect (USADE)

According to ISO 14155:2020: Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

6.1.13 Vital Signs

Vital signs (blood pressure, pulse rate, respiratory rate, body temperature, systolic blood pressure, diastolic blood pressure, oxygen saturation) and anthropometrics (height, body weight, BMI) will be measured at Visit 1 and 2 (height, body weight, and BMI only at Visit 1).

At Visit 2 (transfusion visit) vital sign measurements will be made: before the transfusion, every 15 (+/- 5) minutes during the transfusion, and after the transfusion.

6.1.14 Physical Examination (PE)

A physical examination (General appearance, Respiratory system, Cardiovascular system, Dermatological system and other body system(s)) will be done at Visit-1 (Screening) and Visit-5 (Follow-up 3).

6.2 Laboratory Assessments

6.2.1 Hematology

Hematology including hemoglobin will be measured at three time points:

1. Visit 2 (transfusion visit) at maximum 4 hours before the transfusion to minimum of 15 minutes before transfusion
2. Visit 2 (transfusion visit) at 15 to 60 minutes after the transfusion.
3. Visit 5 (Follow-Up 3)

6.2.2 Arterial Blood Gasses

Assessment of Arterial Blood Gases (ABG) will be performed on the burn patient group only. ABG will be measured at three time points during Visit 2 (transfusion visit):

1. Pre-operative (pre transfusion)
2. Intra-operative (during transfusion)
3. Post operative (post transfusion)

6.2.3 Clinical Chemistry

Clinical Chemistry will be measured at Visit 2, Visit 5 for the hematology patients only.

6.3 Other Assessments

6.3.1 Demographics

Demographics and bassline characteristics will be collected at screening (Ethnicity, Race, Specify, patient group) and for burn patients (Total body surface area of burn).

6.3.2 Eligibility

The eligibility for the two subgroups will be assessed at Visit-1 (screening) and includes:

Hematological malignancies patient group:

1. Male or female patients at least 18 years of age
2. Patients expected to require > 2 units of red blood cells in a single transfusion event
3. Patients who have the capacity to consent to participate and are willing to comply with the study procedures.
4. Patients identified by a Transfusion hemoglobin trigger of less than 9 g/dL
5. Patients with a documented diagnosis of leukemia, myelomatosis or MDS requiring chronic transfusions

Burn patient group:

1. Male or female patients at least 18 years of age
2. Patients who have the capacity to consent by themselves to participate to the clinical investigation
3. Smaller burn patients, hospitalized with a Total Body Surface Area (TBSA%) burn ≥ 10% and ≤ 50%
4. Patients expected to require > 2 unit of red blood cells in a single transfusion event

6.3.3 Concomitant Medications and Medical History

Information on Concomitant Medications will be collected throughout the entirety of the patient's participation in the clinical investigation from Visit 0 (Screening) to Visit 5 (Follow-Up 2). Information on Medical History will be collected at screening.

6.3.4 Duration of Transfusion

Information of the duration of the transfusion(s) will be collected at the Visit 2 (transfusion visit) and will include duration of possible interruption(s).

7 Method of Analysis

7.1 General

All statistical analyses will be performed in accordance with the ICH E9 guideline for Statistical Principles for Clinical Trials (1), using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

7.1.1 Presentation of Results

All results will be presented by patient group and in total, unless stated otherwise. It should be clearly stated which unit applies to each presented variable.

Continuous data will be summarised using descriptive statistics, and the following parameters will be reported:

- number of patients with evaluable observations and missing observations
- arithmetic mean and standard deviation
- median
- first and third quartiles
- minimum and maximum.

Categorical data will be presented using absolute frequency and percentage. When the absolute frequency is zero, the percentage will not be presented. Unless stated otherwise, the denominator for percentage calculations will be the total number of patient s in the applicable analysis set, including patients with missing data. For variables with missing values, the number and percentage of patients with missing values will be presented.

Data will be presented using an appropriate number of decimal places, to ensure that undue precision is not implied (*e.g.,* the number of decimals should not exceed the accuracy of the measuring instrument).. Raw data will be presented with the same number of decimals as collected, and derived data with an appropriate number of decimals based on general practice, mathematical rationale or scientific rationale.

Minimum and maximum values will be presented with the same number of decimals as the analysed variable and the other descriptive statistics will be presented with one decimal more, except for the standard deviation, which will consistently be presented with two additional decimal points compared to the mean of the specific variable. Percentages and proportions will be presented with one decimal.

Mock tables are presented in the Data Display Plan (DDP), which is a supplementary document to this analysis plan. Individual patient data listings will be presented according to the ICH E3 guideline for Structure and Content of Clinical Study Reports (2), unless stated otherwise.

7.1.2 Baseline

Unless stated otherwise, the baseline value for a parameter is defined as the last non-missing value before the transfusion.

7.1.3 Analysis Relative Day

The analysis relative day for an assessment/value is defined as the time in days and hours from the transfusion to the date and hour of the assessment. The date of transfusion is considered as day 1, and earlier dates will correspond to a negative day.

7.1.4 Analysis Visit

An analysis visit is defined as a categorical variable used to classify values within an analysis variable into temporal or conceptual groups used for analyses.

The visits as defined in the case report form, CRF, will be used as analysis visits.

In general, data from unscheduled visits will be presented in data listings only and not included in analysis or summary tables. An exception to this is data used to confirm eligibility in association with screening where the last assessment will be considered in summaries of screening data.

7.1.5 Handling of Missing Data

Data listings will include the observed values.

7.1.6 Subgroups

The following subgroups will be defined as described above in assessments:

- Hematological malignancies patient group
- Burn patient group

The following variables will be analysed for both subgroups:

- Adverse Event (AE)
- Serious Adverse Event (SAE)
- Device deficiency
- Malfunction
- Device deficiency with Serious Adverse Device Effect (SADE)
- Adverse Device Effect (ADE)
- Serious Adverse Device Effect (SADE)
- Causal Relationship of SAE
- Serious Health Threat
- Unanticipated / Unexpected Serious Adverse Device Effect (USADE)
- AEs occurrence
- Hemoglobin (corrected for patient blood volume and hemoglobin dose)
- Vital Signs (VS)

Arterial blood gases will only be analysed on the burn patient group.

7.2 Analysis Sets

The decision on the classification of patient s to each analysis set will be taken at the clean file meeting, and documented in the clean file report together with the reasons for excluding patients from analysis sets.

7.2.1 All Patient s set

Data from all enrolled patients will be included in the analysis. This includes data from patients who withdraw or drop out of the study up to and including their last visit.

7.2.2 Safety Analysis Set

The safety analysis set is defined as all patients who received the transfusion.

7.3 Disposition of Patient s

The following will be presented:

- Number of screened patient s, in total.
- Number of screening failures, in total.
- Based on the number of enrolled patient s, the following will also be presented, by patient group and in total:
- Number and percentage of patients who did not receive the transfusion.

- Number and percentage of patients who received the transfusion.
- Number and percentage of patients who completed the study.
- Number and percentage of patients who withdrew prematurely from the study.
- Number and percentage of patients in each of the analysis sets.

In addition, a frequency table on the primary reason for premature withdrawal from the study will be presented by patient group and in total. Percentages for this table will be based on the number of prematurely withdrawn patients.

The number of patients attending each study visit will also be summarised.

7.4 Protocol Deviations

Protocol deviations will be presented in a data listing.

7.5 Demographics and Baseline Characteristics

Summary statistics and frequencies on demographic data (age, ethnicity, and race) will be presented for all analysis sets together with the baseline characteristics height, weight, and BMI.

7.6 Medical History and Concurrent Diseases

Medical history and concurrent diseases will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For each system organ class and preferred term, the number and percentage of patients with at least one condition in that system organ class or preferred term will be presented. Medical history and concurrent diseases will be presented in separate tables, based on the safety analysis set.

Medical history is defined as events stopped prior to baseline. Concurrent diseases are defined as ongoing events and events stopped on or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the events:

	Imputed start date	Imputed end date
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify the condition based on the reported and/or imputed start and end dates, it will be considered as concurrent. In data listings, the dates will be presented as reported.

7.7 Concomitant Medication

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary and summarised by therapeutic subgroup (ATC level 2) and preferred name.

For each therapeutic subgroup and preferred name, the number and percentage of patients who used at least one medication of that therapeutic subgroup or preferred name will be presented. Prior and concomitant medications will be summarised in separate tables, based on the safety analysis set.

If a reported medication cannot be coded with a preferred name, the lowest available higher-level dictionary term will be used instead in the summary tables. If a medication cannot be coded on a lower level than the therapeutic subgroup or the anatomical main group (ATC level 1), that medication will be presented as ‘Not codable’ under that therapeutic subgroup/anatomical main group.

Concomitant medication is defined as ongoing medication or medication stopped on or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the medication:

	Imputed start date	**Imputed end date**
Unknown year	Missing	Missing

Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify a medication based on the reported and/or imputed start and end dates, it will be considered as concomitant. In data listings, the dates will be presented as reported.

7.8 Safety Evaluation

7.8.1 Adverse Events

An overview of all adverse events for both patient groups will be presented, including the number and percentage of patients with at least one, and the total number, of the following:

- Adverse Event (AE) overall up to 7 days (+/- 1 day) after the transfusion.
- Adverse Event (AE) (all types/grades) within a time frame up to 24 hours following the transfusion.
- Adverse event from enrolment up to 7 days (+/- 1 day) following the transfusion
- Adverse event overall
- Serious Adverse Event (SAE)
- Any adverse event leading to withdrawal of the study treatment.
- Adverse Event broken down by relationship to the medical device (Not related, Possible, Probable, Causal relationship).
- Adverse Event broken down by relationship to the study procedure (Not related, Possible, Probable, Causal relationship)
- Adverse Event broken down by severity (Catastrophic, Critical, Serious, Minor, Negligible).
- Any other medication or treatment given because of the occurrence of the adverse event.
- AE broken down by outcome (Fatal, Not recovered/not resolved, Recovered/resolved, Recovered/resolved with sequelae), Recovering/resolving, Unknown).

The incidence of adverse events will be presented by system organ class and preferred term. For each system organ class and preferred term, the total number of adverse events as well as the number and percentage of patient s with at least one adverse event in that system organ class or preferred term will be presented. The incidence of serious adverse events will be presented in the same way.

Separate tables for the incidence of adverse events broken down by severity and the incidence of adverse events broken down by causality assessment (to medical device as well as to study procedure) will also be presented by system organ class and preferred term.

All AEs recorded in the study will be presented in listings.

7.8.2 Adverse Device Effect

An overview of all adverse device effects for both patient groups will be presented, including the number and percentage of patient s with at least one, and the total number, of the following:

- Adverse Device Effect (ADE) overall up to 7 days (+/- 1 day) after the transfusion.
- Adverse Device Effect (ADE) (all types/grades) within a time frame up to 24 hours following the transfusion.
- Serious Adverse Device Event (SAE)
- Any adverse device event from enrolment up to 7 days (+/- 1 day) following the transfusion
- Any adverse device event overall

- Device Deficiency
- Malfunction of Device
- Action taken because of the Adverse Device Effect
- Medication or treatment given because of the Adverse Device Effect
  .
- Adverse Device Effect broken down by Severity.
- Serious Adverse Device Effect broken down by Anticipation
- Adverse Device Effect broken down by Relationship to medical device.
- Adverse Device Effect broken down by Relationship study procedure.
- Adverse Device Effect broken down by Seriousness.

The incidence of adverse device events will be presented by system organ class and preferred term. For each system organ class and preferred term, the total number of adverse events as well as the number and percentage of patient s with at least one adverse event in that system organ class or preferred term will be presented.

7.8.3 The decision regarding the classification of Unanticipated/Anticipated Adverse Device Effects will be made during the clean file meeting.Hemoglobin Evaluation

Summary statistics on the Hemoglobin test result will be presented by visit and by time point. For post-baseline visits, summary statistics on the change from baseline will also be presented. A frequency table on the clinical interpretation of Hemoglobin test results (*e.g.,* normal, abnormal but not clinically significant, abnormal and clinically significant) will be presented by visit. For the post transfusion evaluation, the shift from baseline will also be presented.

Summary statistic on the Hemoglobin level before the following transfusion will also be presented, defined as the Hemoglobin assessment conducted immediately prior to the upcoming transfusion or the Hemoglobin assessment at Visit 5.

Test results reported in other units will be converted from their original units to the standardised unit g/dL, using appropriate conversion factors. Data listings will include test results in both original and standardised units.

Any value reported as below the lower limit of quantification or as undetectable will be considered as missing, and any value reported as above the upper limit of quantification will be considered as being equal to the upper limit. The reported value will be presented in data listings.

7.8.4 Vital Signs

For vital signs (VS) parameters, summary statistics will be presented by the visit except for Visit 2 (transfusion visit) where VS will be presented by pre, during (15-minute time intervals) and post transfusion. For post-baseline visits, summary statistics on the change from baseline will also be presented.

7.8.5 Arterial Blood Gases Evaluation (Burn patients group only)

Summary statistics on the Arterial Blood Gases test results will be presented by visit. For post-baseline visits, summary statistics on the change from baseline will also be presented. Frequency tables on the clinical interpretation of Arterial Blood Gases test results (*e.g.,* normal, abnormal but not clinically significant, abnormal, and clinically significant) will be presented by visit. For the post transfusion evaluation, the shift from baseline will also be presented.

Each Arterial Blood Gas parameter will be presented in a separate table. A list of all Arterial Blood Gas parameters (including specification of the standardised units to be used for analysis) is presented below.

Arterial Blood Gases (Burn patients group only)
pH

pO2 kPa
pCO2 kPa
HCO3 mmol/L
Base (excess) mmol/L

7.8.6 Hematology and Blood chemistry

Hematology and blood chemistry data is exclusively gathered as a backup for AE findings and will not be incorporated into the analysis. Consequently, no summary tables for hematology or blood chemistry test results will be generated, except for hemoglobin as described above. The presentation of test results will be limited to listings only.

7.8.7 Physical Examination

For all body systems examined, frequency tables on the investigator's assessment will be presented by visit. For post-baseline visits, the shift from baseline will also be presented.

8 Changes to Planned Analysis

8.1 Exclusion and modification of secondary objectives

Two of the secondary objectives have been modified or excluded

- *"Assessment of AEs occurrence up to 7 days (+/- 1 day) post transfusion, in comparison with historical control (including but not limited to infection, deep vein thrombosis, acute respiratory distress syndrome, transfusion-related acute lung injury, transfusion associated circulatory overload, anaphylactic shock, acute haemolytic transfusion reaction)"* Outcome 1 has been revised to "*Assessment of AEs occurrence up to 7 days (+/- 1 day) post transfusion (including but not limited to infection, deep vein thrombosis, acute respiratory distress syndrome, transfusion-related acute lung injury, transfusion associated circulatory overload, anaphylactic shock, acute haemolytic transfusion reaction)"*. The reason for the change is that data on historical control is not available.

- "*Hemoglobin increment from transfusion corrected for patient blood volume and hemoglobin dose"* Has been replaced with "E*valuation of blood pH, pO2, pCO2, HCO3 and base (excess) before, during and after the transfusion."*

8.2 Allowing for time intervals in vital signs (VS) measurements.

Instead of presenting VS measurements every 15 minutes during and after the transfusion, they will be presented within 15-minute time intervals. If two measurements fall within the same interval, the measurement closest to the intended assessment time will be used.

9 Derived Variables

9.1 Disposition of Patient s

A screening failure is defined as a screened but not randomised patient.

9.2 Demographics and Baseline Characteristics

9.2.1 Age

Age will be computed as the integer part of the time in years between the year of birth and the date the written informed consent was signed, using the SAS function yrdif() with the basis parameter set to 'age'.

9.2.2 Body Mass Index

BMI will be computed as the body weight in kg divided by the squared height in metres.

9.3 Change from Baseline

Change from baseline will be computed as the difference between a post-baseline value and the corresponding baseline value.

Percentage change from baseline will be computed as 100 times the change from baseline divided by the baseline value.

9.4 Duration

The Duration of the transfusion in hours and minutes will be computed as the time in hours and minutes from the start of the transfusion to the end of the transfusion excluding possible interruptions.

10 References

1. ICH Harmonised Tripartite Guideline for Statistical Principles for Clinical Trials E9. February 1998.

2. ICH Harmonised Tripartite Guideline for Structure and Content of Clinical Trial Reports E3. November 1995.

11 Signoff

We have read this SAP for the HEM001 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hemanext: [redacted]

SIGNATURE AND DATE	[redacted]

LINK Medical SAP Author: [redacted]

SIGNATURE AND DATE	DocuSigned by: [redacted] 6/24/2024

LINK Medical SAP Approver [redacted]

SIGNATURE AND DATE	DocuSigned by: [redacted] 6/25/2024

12 Appendices

Appendix A: Clinical investigation flow chart Hematogical Malignancies Group:

Investigation Periods	Screening & Enrollment Visit	Pre-Transfusion	Transfusion	Post-Transfusion	Follow Up 1	Follow-up 2	Follow-up 3
Visit	1	2	2	2	3	4	5
Time (hour, day, week)	D0	D1	D1	D1	D2 (≤ 24h)	D7 (+/- 1 day)	Day of subsequent transfusion or D28, whichever comes 1st
In- /Exclusion Criteria	x	x					
Patient Information							
Patient consent (ICF)	x						
Demographics	x						
Medical History	x						
Concomitant Medications	x	x	x	x	x	x	x
Physical Examination	x						x
Pregnancy Test	x						
Height	x						
Weight	x						
RBC Unit Weight		x					
Patient Hemoglobin		x		x			x
Blood Pressure	x	x	x	x			
Heart Rate	x	x	x	x			
Body Temperature	x	x	x	x			
Respiratory Rate	x	x	x	x			
Oxygen Saturation	x	x	x	x			
Transfusion			x				
Adverse Events, Adverse device effects	x	x	x	x	x	x	x
Review Device Integrity		x	x	x			
Patient Diary	x	x	x	x	x	x	

Appendix B: Clinical investigation flow Burn patients Group:

Investigation Periods	Screening & Enrollment Visit	Pre-Transfusion	Transfusion	Post-Transfusion	Follow Up 1	Follow-Up 2	Follow-Up 2
Visit	1	2	2	2	3	4	5
Time (hour, day, week)	Day 0	Day 1	Day 1	Day 1	Day 2 (≤ 24 h)	Day 7 (+/- 1 day)	Day of subsequent transfusion or D28, whichever comes 1st
In- /Exclusion Criteria	x						
TBSA	x						
Patient Information							
Patient information and consent (ICF)	x						
Demographics	x						
Medical History	x						
Concomitant Medications	x	x	x	x	x		x
Physical Examination	x						x
Pregnancy Test	x						
Height	x						
Weight	x						
RBC Unit Weight		x					
Patient Hemoglobin		x		x			x
Blood Pressure	x	x	x	x			
Heart Rate	x	x	x	x			
Body Temperature	x	x	x	x			
Respiratory Rate	x	x	x	x			
Oxygen Saturation	x	x	x	x			
Transfusion			x				
Adverse Events, Adverse device effects	x	x	x	x	x		x
Review Device Integrity		x	x	x			