CLI 00126

RedeS PROTOCOL, v9.0

A Randomized, Double-Blind, Controlled, Parallel Group Study with the INTERCEPT Blood System for Red Blood Cells in Regions at Potential Risk for Zika Virus Transfusion-Transmitted Infections (RedeS)

December 18, 2023

NCT03037164

PROTOCOL

TITLE: A Randomized, Double-Blind, Controlled, Parallel Group Study with the INTERCEPT Blood System for Red Blood Cells in Regions at Potential Risk for Zika Virus Transfusion-Transmitted Infections (**RedeS** Study)

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SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
CERUS CORPORATION</td><td colspan="2">Individual Study Table Referring to Part of the Dossier</td><td>(For National Authority Use only)</td></tr>
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Not applicable</td><td>Volume:</td><td></td><td rowspan="3"></td></tr>
<tr><td>Name of Active Ingredient:
Red Blood Cells treated with the INTERCEPT Pathogen Reduction System</td><td>Page:</td><td></td></tr>
<tr><td>Title of Study:</td><td colspan="3">A Randomized, Double-Blind, Controlled, Parallel Group Study with the INTERCEPT Blood System for Red Blood Cells in Regions at Potential Risk for Zika Virus Transfusion-Transmitted Infections (RedeS Study) – CLI 00126</td></tr>
<tr><td colspan="4">Investigators / Study Sites:
• Up to 800 subjects at 15 clinical sites</td></tr>
<tr><td colspan="4">Publication (reference): NA</td></tr>
<tr><td colspan="2">Study period (years):
Date of first enrollment: 03 April 2017
Date of last completed: TBD</td><td colspan="2">Phase of development: Phase 3 with an extension period for chronically transfused subjects.</td></tr>
<tr><td colspan="4">Objectives:
Rationale:
The primary purpose of this study is to evaluate the safety of the INTERCEPT Blood System for Red Blood Cells pathogen reduction technology (PRT) in comparison to conventional RBCs in patients who require acute and long-term RBC transfusion support in areas at risk of transfusion transmitted infections (TTI).</td></tr>
<tr><td colspan="4">Methodology: Study Design:
• Multi-center, randomized, double-blind, active-controlled, parallel-design study, with an extension option to evaluate patients requiring repeated transfusion for chronic anemia or sickle cell disease (SCD) patients undergoing regular repeated red cell exchange (RCE).</td></tr>
<tr><td colspan="4">Endpoints:
Primary
• Efficacy (all non-bleeding patients at baseline, excluding RCE patients):
o Adjusted hemoglobin increment, defined as the difference between the pre-transfusion and post-transfusion episode hemoglobin values divided by the total hemoglobin content transfused, averaged over one or more transfusion episodes in patients without active bleeding at baseline (active bleeding is defined as WHO Grade 3 or 4 bleeding).
• Safety (all patients):
o Proportion of patients with any treatment-emergent adverse events (TEAEs) possibly, probably, or definitely related to study RBC transfusion through 28 days after the last study transfusion.
o Proportion of patients with treatment-emergent antibodies with confirmed specificity to IBS RBCs
Secondary
• Efficacy (all non-bleeding, chronically transfused patients in 28-day acute and 28-day +6-month extension study, excluding RCE patients):</td></tr>
</table>

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- Adjusted hemoglobin consumption, defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (g/kg/day), in patients without active bleeding at baseline.

- Efficacy (SCD patients enrolled into the 28-day +6-month extension for three RCE procedures):
  - HbA clearance in patients with SCD undergoing regular repeated RCE.

- Safety (all patients):
  - Treatment-emergent AEs (TEAEs) for 28 days after last study transfusion;
  - Transfusion reactions related to study RBCs (test or control) (as defined by the CDC National Healthcare Safety Network [NHSN] Hemovigilance Module protocol), for 28 days after the last study transfusion;
  - Treatment-emergent immunization to RBC allo-antigens; and
  - All-cause mortality through 28 days after the last study transfusion
- Safety (SCD patients enrolled into the 28-day + 6-month extension for three RCE procedures):
  - Proportion of subjects with adverse events of special interest (AESI) through 28 days after the last study transfusion.
  - S-300 and Glutathione (GSH) plasma levels before and 15 minutes to 4 hrs after RCE.

Sample Size and Power Calculation:

The study will aim to include 468 non-bleeding patients, excluding RCE patients (approximately 234 per treatment group) with evaluable data on the primary efficacy endpoint of adjusted hemoglobin increment and will have approximately 90% power to declare non-inferiority for the primary efficacy endpoint in non-bleeding patients with a non-inferiority margin of 15% of the control mean at the two-sided 0.05 alpha level, assuming no true treatment difference and a coefficient of variation of 50%.

In addition, up to 30 SCD patients requiring regular repeated RCE will be enrolled into the 28-day +6-month extension period to allow a total of three consecutive RCE procedures in at least 20 transfused evaluable patients.

It is estimated that between 600 to 800 randomized and transfused patients will be needed to meet the targets for sample size to power the primary efficacy endpoint and the 28-day +6-month extension period enrollment goals. The planned sample sizes may not provide adequate power to demonstrate non-inferiority of IBS RBC for the secondary efficacy endpoint of adjusted hemoglobin consumption at the pre-specified 15% non-inferiority margin.

Diagnosis and main criteria for inclusion:

Inclusion criteria

For all enrolled patients:

- Age ≥ 4 years.
- Patients who require or are expected to require a transfusion of RBC component(s), including red cell exchange transfusion.
- Signed and dated informed consent form.

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- Female patients of child-bearing potential must:
  - Have negative serum or urine pregnancy tests performed at the Screening visit within 30 days of randomization to rule out pregnancy, and
  - Agree to use to use at least one method of birth control that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner for the duration of study participation and an additional 28 days.

For 28-day +6-month extension study in patients requiring repeated simple transfusions:

- A diagnosis of a bone marrow failure syndrome requiring repeated RBC transfusion for congenital or acquired chronic anemia (e.g., sickle cell anemia, thalassemia, other hemoglobinopathies, myelodysplastic syndrome, aplastic anemia, chemotherapy or stem cell transplant etc.).

For 28-day +6-month extension study in SCD patients requiring regular repeated RCE:

- Diagnosis of SCD, either HbSS, HbSC or HbSB0 thalassemia, confirmed by Hb electrophoresis, deoxyribonucleic acid (DNA) analysis or high-performance liquid chromatography (HPLC)
- Currently participating in an automated RCE transfusion program (for at least 3 months prior to enrollment) with 3- to 8-week intervals between RCE episodes.

Exclusion criteria:

- Confirmed positive baseline serum/plasma antibody specific to IBS RBC (S-303 treated RBC) as determined by INTERCEPT S-303 antibody screening panel prior to receiving the first study transfusion
- Pregnant or breast feeding.
- Presence of an RBC warm autoantibody with evidence of active hemolysis.
- Positive DAT as defined below:
  - A polyspecific-DAT reaction strength > 2+, or
  - A polyspecific-DAT (any strength) in conjunction with pan-reactivity with a commercial IAT antibody screening panel that precludes the identification of underlying alloantibodies or indicates the presence of autoantibody.
- Have received investigational products, including investigational blood products, pharmacologic agents or imaging materials, within 28 days prior to randomization. Prior receipt of conventional blood products tested with an investigational NAT test is not considered ground for exclusion.
- Patients presenting with or expected to have massive hemorrhage (≥10 RBC units within 24 hours) or expected to require massive transfusion protocols. Planned RCE does not apply.
- Patients who require neonatal transfusions and intrauterine transfusions.
- Pre-existing antibody to RBC antigens that may make the provision of compatible study RBC components difficult.
- History of transfusion reactions requiring washed RBCs, volume reduced RBC, or RBCs with additive solution removed.
- Patients with documented IgA deficiency or a history of severe allergic reactions to blood products.

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- For SCD patients to be enrolled into the 28-day +6-month repeated RCE arm of the study:
  - A history of acute chest syndrome in the last 6 months, or hyperhemolysis syndrome at any time.
  - Clinical evidence of splenic hyperfunction or splenic enlargement: ≥18 cm in longitudinal diameter (diagnosed at the Investigator's discretion according to the data available, with ultrasound data being preferable).
  - Currently receiving chemotherapy for treatment of cancer. Hydroxyurea for SCD is acceptable if subject has been on stable therapy for 3 months and no changes to dosage are planned.
  - Subject is in active treatment with renal dialysis.
  - Any subject for whom a substantial change in the number of RBC components transfused is anticipated due to anticipated splenectomy, bone marrow transplant, surgery or other change in clinical status.
  - Subject with known G6PD deficiency or requiring treatment with medications that are known to adversely affect RBC viability or bone marrow function.

Test Product, dose and mode of administration

The test device is the INTERCEPT Blood System (IBS) for RBC. The INTERCEPT treatment process will be performed on leukocyte reduced RBC components in AS-5 additive solution (or SAG-M at non-US sites) prepared from whole blood collections from qualified blood donors; and stored in SAG-M additive solution. The test components are allogeneic IBS RBC components stored at 1°C to 6°C for up to 35 days post-donation and administered intravenously. Test RBC components will be labeled in a manner so as to maintain blinding. Test products may be irradiated, if indicated by the treating physician. Dose and schedule of RBC transfusions will be determined by the treating physician.

Control Product (Reference therapy), dose and mode of administration

The Control transfusion components are conventional leukocyte reduced RBC components in AS-1, AS-3 or AS-5 (or SAG-M at non-US study sites) stored at 1°C to 6°C for up to 35 days post-donation and administered intravenously. The Control RBC components will be labeled in a manner so as to maintain blinding. Control products may be irradiated as required. Dose and schedule of RBC transfusions will be determined by the treating physician.

Study Procedures

Patients will be approached, consented, screened for eligibility and randomized to receive either Test or Control RBCs in one of the three arms at the beginning of the study:

- Bleeding or non-bleeding patients at baseline may be enrolled into the acute 28-day transfusion period.
- Non-bleeding patients at baseline with chronic anemia requiring repeated simple transfusion may be enrolled into the 28-day +6-month extension period.
- SCD on a regular repeated RCE program at baseline may be enrolled into 28-day +6-month extension period to receive a total of 3 consecutive RCE procedures.

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Eligible patients will be randomized and transfused with study RBCs (Test or Control with 1:1 ratio) according to local practices for up to 28 days of transfusion support. Following the 28-day acute transfusion support period, patients will be transfused with conventional RBC components as indicated by their treating physician unless they were enrolled at baseline in the optional 6-month extension period.

Non-bleeding patients at baseline requiring repeated RBC transfusion for congenital or acquired chronic anemia (e.g., sickle anemia, thalassemia, other hemoglobinopathies, myelodysplastic syndrome, aplastic anemia, chemotherapy or stem cell transplant etc.) will be eligible to participate in an extension option for up to 6 months or up to 10 transfusion episodes, whichever occurs first, to evaluate patients requiring repeated transfusion for chronic anemia.

In addition, SCD patients on a regular RCE program at 2 or more clinical sites may be enrolled at baseline into the 6-month extension period to receive up to a total of 3 consecutive RCE procedures.

Study procedures are summarized as follows:

Screening/Recruitment

All potentially eligible patients at participating institutions will be approached for study consent. Subjects <18 years of age will require subject assent and parental consent. For subjects eligible for enrollment into the 6-month extension period option, consent/assent for the extension period should be obtained at initial enrollment.

Patients who consent to the study will be assigned a study ID number and undergo screening. Screening data collection and procedures will include:

Demographics (age, sex), vital signs, height, weight, indication for anticipated transfusion, type of scheduled surgery (if applicable), medical and surgical history, transfusion history, physical examination, comorbid conditions, concomitant medications, hematology panel, blood type and Rh, Indirect Antiglobulin Test (IAT), blood chemistry, coagulation panel, Direct Antiglobulin Test (DAT), immune reactivity to IBS RBCs (if available), pregnancy test (when applicable). Once all screening assessments are completed and eligibility is confirmed, the subject may be randomized.

For SCD patients on a regular RCE program, if available in the medical record, the pre- and post- RCE total Hemoglobin, HbA, HbS and HbF concentrations should be recorded for up to 6 months prior to the first study transfusion.

If results from the Screening assessments listed in Table 7-1, Table 7-2 and 7-3 are available in the medical record within 30 days prior to randomization, those data may serve as the screening data and the assessments do not need to be repeated unless the subject has an RBC transfusion in the 30-day period.

If an RBC transfusion occurs after determined eligibility but prior to randomization, the subject may be randomized and those Screening assessments listed in Table 7-1, Table 7-2 and 7-3 should be repeated prior to the first study transfusion.

A pregnancy test (when applicable) must be performed at the Screening visit within 30 days of randomization.

Randomization and Blinding

Potential patients will be consented and begin screening in the study in order to determine eligibility for inclusion in one of the three study arms.. An Interactive Web Response System (IWRS) will be used for electronic randomization of eligible patients to receive Test or Control RBCs.

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Randomization will be at a 1:1 ratio of Test: Control and stratified by site, baseline bleeding status [indication for RBC transfusion due to active bleeding (WHO Grade 3 or 4, **APPENDIX 5**) or for anemia without active bleeding], patients' participation in the optional extension period (yes/no) and patients' need for RCE. Anticipated surgical bleeding and planned blood loss/replacement through RCE at baseline should be included as active bleeding (Grade ≥3) by definition. Randomized patients who do not receive any study RBC transfusions through 28 days after randomization will be withdrawn from the study and replaced. Additional data will not be collected for these patients. These subjects may be reassessed for eligibility and re-enrollment after withdrawal.

At the end of screening, the patient's eligibility status will be entered into the electronic data capture system (EDC). If eligible, the patient will be randomized. Only appropriate blood bank staff will be able to access the treatment arm assignment. Study RBC unit labels will be indistinguishable for Test and Control products. Medical staff, and others caring for participating patients, as well as the sponsor (and delegates) will be blinded to treatment assignment. Unblinded delegates will monitor the production of the RBC components at designated blood centers.

Treatment

Repeated Simple Transfusion Arm

In the initial acute transfusion period, randomized patients will be transfused with Test or Control RBC components for up to 28 days. If the patient is entered into the optional extension period, randomized patients will be transfused with Test or Control RBC components for an additional 6 months, or up to 10 transfusion episodes, whichever occurs first. Subjects participating in optional extended study will continue to receive the same study RBCs (Test or Control) as in their initial 28-day study period for up to 10 transfusion episodes. Patients will be transfused with conventional RBC components as indicated by their treating physician once the 10 transfusion episodes or 6 months has been completed.

An RBC transfusion episode is defined to include consecutive RBC units transfused until the next post-transfusion Hb determination with ≤12 hours between transfusions (from the end of a prior component transfused to the start of a subsequent component transfused).

RCE Arm

SCD patients on a regular RCE program enrolled into the 6-month extension period will receive 3 consecutive RCE procedures with study RBC with an interval of 3-8 weeks between RCE procedures, as determined by their physician.

A confirmed negative immune reaction to IBS RBC is required prior to the first study transfusion/RCE and at every time point a Type and Screen (IAT) is performed for a patient within the 28-day acute transfusion period or during the extension period. Compatibility for RBC antigens will be confirmed using site's SOPs prior to transfusion of study RBCs. In case of confirmed physiologically active antibodies to IBS RBC or any presumed or documented antibodies to IBS RBC that preclude further transfusion with study RBCs, patients will be withdrawn from the study treatment and supported with conventional RBC components and followed for safety. Patients with antibodies to IBS RBC will be investigated for evidence of hemolysis and continue with all planned visits and safety monitoring.

Study Assessments: Monitoring and Follow-up

The acute transfusion support period will comprise 28 days from the day of the first study transfusion (Day 1)

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through Day 28, or death. For subjects enrolled in the optional extension period, they will receive transfusion support for an additional 6-months.

During these periods, patients enrolled into the 6-month repeated simple transfusion arm will receive as many study RBCs as deemed appropriate by the treating physician for up to 10 transfusion episodes. Patients enrolled into the 6-month RCE arm will receive 3 consecutive RCE. All adverse events (AE), serious AE (SAE), transfusion reactions (TR) and unanticipated adverse device effects (UADE) will be collected starting from the initiation of the first study transfusion through exactly 28 days after the last study transfusion or death, whichever occurs first. The Investigators will assess each AE/SAE/TR/UADE for relation to the transfused study RBCs. TR will be classified by the definitions in the CDC NHSN Hemovigilance Module Surveillance Protocol (**APPENDIX 1, 2 & 3**) and will be captured in the eCRF and in the CDC NHSN Biovigilance Component/Hemovigilance Module, if in routine use by the site (**www.cdc.gov/nhsn**).

Most proximate vital signs in the medical record will be collected prior to and following each study transfusion. The subject's hemoglobin value will be collected from the medical record, or if not available, a study sample will be submitted for testing, prior to and following each study transfusion episode/RCE within 15 minutes to 24 hours after the end of the transfusion episode and before the next RBC transfusion.

Relevant concomitant medications taken during the study and blood products transfused will be recorded with indication, total daily dose, and dates of drug administration.

During the acute transfusion period, patients will undergo the following assessments prior to each transfusion episode: vital signs, AEs, TRs, SAEs and UADEs, comorbid conditions, blood samples for safety labs (hematology panel, blood chemistry panel), IAT and immune reactivity to IBS RBCs. Samples may be used for additional in vitro research tests as required to confirm transfusion-transmitted infections.

An immune reactivity to IBS RBCs test will be performed and resulted each time an IAT is performed within the 28-day acute and 6-month extension transfusion support period.

RCE Arm

The following parameters should be assessed before and 15 mins to 4 hours after each RCE procedure:

- Hematology panel
- Reticulocytes
- % of HbS, HbA, and HbF
- Coagulation panel.
- Plasma frozen sample for determination of S-300 and GSH concentrations

Day 14 (±7 days) after each RCE procedure for SCD patients undergoing regular RCE:

- Hematology panel
- Reticulocytes
- % of HbS, HbA, and HbF

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Follow-Up Period for all transfused patients

For the purposes of the Day 28 (<u>± *7 days*</u>) and Day 75 (<u>± *15 days*</u>) follow-up visits, Day 1 of the follow-up period is the day after the last study transfusion, either in the initial 28-day acute transfusion period or, if the subject is entered, in the optional extension period.

Day 28 (± 7 days) after the last study transfusion or before first post-study RCE with conventional RBCs in patients on a regular RCE program

Vital signs will be collected, and blood samples will be collected for:

- Hematology panel
- Blood chemistry panel
- Coagulation panel
- DAT and IAT
- Immune reactivity test for IBS RBC
- In addition for SCD patients undergoing regular RCE:
  - Reticulocytes
  - % of HbS, HbA, and HbF
  - Plasma frozen sample for determination of S-300 and GSH concentrations.

All AEs, SAEs, TRs and UADEs will be reviewed and recorded for the period from the first study transfusion through exactly 28 days after the last study transfusion.

End of Study Visit Day 75 (±15 days) after the last study transfusion) for all transfused patients

Blood samples will be collected for:

- DAT
- Immune reactivity test for IBS RBC.

Data and Safety Monitoring Board (DSMB)

The study will be monitored by an independent Data and Safety Monitoring Board, that will meet after approximately 300 patients are treated and at any other time that safety or enrollment rate concerns arise and as defined in the DSMB charter. In this interim safety data review, the DSMB will assess safety data summarized in a group-blinded manner. Enrollment and study transfusions will continue during the interim safety review, unless otherwise advised by the DSMB.

Stopping Rules

Specific stopping rules based on development of immune reactivity to IBS RBCs are defined in **Section 5** of the protocol.

Criteria for evaluation:

Efficacy:

Acute Simple Transfusion and Repeated Simple Transfusion Arms

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The primary efficacy measure (evaluated in all non-bleeding patients at baseline, excluding RCE patients) is the adjusted hemoglobin increment, defined as the difference between the pre-transfusion episode and the post-transfusion episode hemoglobin values (taken within 15 minutes to 24 hours of the end of a transfusion episode, before the next transfusion) divided by the total hemoglobin content transfused, averaged over one or more transfusion episodes in patients without active bleeding at baseline (active bleeding is defined as WHO Grade 3 or 4 bleeding). Anticipated surgical bleeding and planned blood loss/replacement through red cell exchange at baseline should be included as active bleeding (Grade ≥3) by definition.

The secondary efficacy endpoint (evaluated in all non-bleeding, chronically transfused patients in 28-day +6-month extension study, excluding RCE patients) is the adjusted hemoglobin consumption, defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (g/kg/day), in patients without active bleeding at baseline.

RCE Arm

For SCD patients enrolled into 28-day +6-month extension for three RCE procedures, the efficacy assessment is a comparison of the mean of the difference in the HbA clearance rate (g/dL/day) between the Test subjects (INTERCEPT RBC) versus the Control subjects (conventional RBCs) in patients who receive 3 consecutive study RCE procedures.

Safety:

All Transfused Patients

The primary safety endpoints (evaluated in all patients) are:

- The proportion of patients with treatment-emergent Adverse Events possibly, probably, or definitely related to study RBC transfusion through 28 days after the last study transfusion;
- The proportion of patients with treatment-emergent antibodies with confirmed specificity to IBS RBCs.

Additional safety assessments (evaluated in all patients) will include, but not be limited to:

- Treatment-emergent adverse events through 28 days after the last study transfusion;
- Transfusion reactions related to study RBCs (test or control) (as defined by the CDC NHSN Hemovigilance Module Surveillance Protocol) through 28 days after the last study transfusion;
- Treatment-emergent immunization to RBC alloantigens;
- Mortality from any cause through 28 days after last study transfusion.

RCE Arm

- For SCD patients enrolled into the 28-day +6-month extension for three RCE procedures:
  - Proportion of subjects with adverse events of special interest (AESI) through 28 days after the last study transfusion;
  - S-300 and Glutathione (GSH) plasma levels before and 15 minutes to 4 hrs after RCE.

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Statistical methods:

The primary efficacy endpoint is defined as the difference between the pre-transfusion episode and the post-transfusion episode hemoglobin values (taken within 15 minutes to 24 hours of the end of a transfusion episode, before the next transfusion) divided by the total hemoglobin content transfused, averaged over one or more transfusion episodes in patients without active bleeding at baseline (hereafter referred to as non-bleeding patients, and active bleeding defined as WHO Grade 3 or 4 bleeding).

The secondary efficacy endpoint is the adjusted hemoglobin consumption (g/kg/day), defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (that is, 28 days for the initial acute period plus 6 months for the extension period if applicable, unless patients prematurely discontinue from the study), in non-bleeding patients. Non-study RBCs received during the study transfusion period will be included to calculate the total hemoglobin content transfused for the two efficacy endpoints in the modified Intention to Treat (mITT) analysis set. Patients receiving non-study RBC transfusions during the study transfusion period will be excluded from the Per Protocol (PP) analysis set. Data from the initial 28-day period and the optional extension period will be summarized separately as well as combined in the final report.

Treatment difference in the adjusted hemoglobin increments and consumption will be evaluated using a non-inferiority test, with a non-inferiority margin of a 15% relative difference between the mean values of Test and Control.

For the primary efficacy endpoint, its primary analysis will be conducted in non-bleeding, modified intent-to-treat (MITT) patients who participate in the initial 28-day period and will utilize data from the initial 28-day acute transfusion period and the extension transfusion period, if applicable.

Specifically, an analysis of variance (ANOVA) model will be used to estimate the mean treatment differences while controlling for the clinical site.

For the secondary efficacy endpoint, its primary analysis will be conducted in non-bleeding MITT patients who participate in the initial and extension periods and will utilize integrated data from both periods.

For the adjusted hemoglobin consumption, the upper bound of a two-sided 95% confidence interval for the treatment difference (Test – 1.15 x Control) less than or equal to zero will result in the rejection of inferiority null hypothesis and the conclusion of non-inferiority.

For SCD patients enrolled into the 6-month extension for three RCE procedures, HbA clearance rate (g/dL/day) will be estimated from the area under the curve (AUC) calculated by the trapezoidal rule based on measurements from post-transfusion samples, 14 ±7-days and pre-transfusion sample from the next scheduled transfusion, adjusted by the duration in days used to calculate the AUC (i.e., between the 15 minutes to 4-hour post-transfusion sample and pre-transfusion sample of the next transfusion) and averaged over all study RCE procedures for each patient. This is a hypothesis generating analysis. Data will be summarized descriptively, and by age group (≤ 18 years old vs. > 18 years old) as applicable. The estimated treatment difference and variability of the outcome measures may be considered for future study planning.

The primary safety measures are the proportion of patients with treatment-emergent AEs possibly, probably or definitely related to study RBC transfusion through 28 days after the last study transfusion and the proportion of

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patients with treatment-emergent antibodies with confirmed specificity to IBS RBCs.

Treatment-emergent AEs and AESIs, will be summarized by treatment group, system organ class (SOC), and preferred term (PT). The proportion of patients with AEs possibly, probably, or definitely related to study RBC transfusions will be compared between treatment groups using a CMH test (controlling for clinical site and baseline bleeding status). The relative risk (Test/Control) and associated confidence interval will also be reported. In the event of sparse counts, Fisher's exact test may also be used to provide statistical interpretation.

Subjects who receive 3 or more study RBC transfusion episodes and have an assessment of antibodies after the third study transfusion episode will be summarized as a subgroup representing subjects who are repeatedly exposed to study RBC in terms of immunogenicity.

To investigate the potential impact of irradiation, subgroup analysis by irradiation status (yes vs. no) may be presented for the primary efficacy endpoint and selected safety data (including SAE, AE, and potassium levels). Subgroup analyses by clinical site, age group (<18, 18-64, and ≥65 years old), sex, and race (white vs. other races) will be conducted, as appropriate.

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHTR	Acute Hemolytic Transfusion Reaction
BVDV	Bovine Viral Diarrhea Virus
C	Celsius
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CHIKV	Chikungunya Virus
CMH test	Cochran-Mantel-Haenszel test
CPD	Citrate Phosphate Dextrose
^{51}Cr	Radiolabeled chromium
eCRF	Electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
DAT	Direct Antiglobulin Test. Also referred to as the direct Coombs test.
Device	The failure of a medical device to function according to its Malfunction requirements.
DENV	Dengue Virus
DHBV	Duck Hepatitis B Virus
DHTR	Delayed Hemolytic Transfusion Reaction
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DSTR	Delayed Serological Transfusion Reaction
EDMS	Electronic Document Management System

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EC	Ethics Committee
FNHTR	Febrile Non-hemolytic Transfusion Reaction
G6PD	Glucose 6-phosphate dehydrogenase
GCP	Good Clinical Practice
GSH	Glutathione (γ-glutamylcysteinyl-glycine)
h	Hour
Hb	Hemoglobin
Hct	Hematocrit
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTR	Hemolytic Transfusion Reaction
IAT	Indirect Antiglobulin Test (also referred to as the Indirect Coombs test)
IBS	INTERCEPT Blood System
IBS RBC	RBC components that have been processed with the INTERCEPT Blood System for Red Blood Cells. Also called S-303 RBC.
ICH	International Conference on Harmonization
IRB	Institutional Review Board
kg	Kilogram
mL	Milliliter
mM	Millimolar
µM	Micromolar
mITT	Modified Intent-to-Treat
N	Number
NCI	National Cancer Institute
NHSN	National Healthcare Safety Network

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PP	Per protocol
RBC	Red Blood Cell
RCE	Red Cell Exchange
RNA	Ribonucleic Acid
S-300	(N-(9-Acridinyl)-ß-alanine). The primary decomposition product of S-303.
S-303	[N,N-bis (2-chloroethyl)]-2-aminoethyl 3-[(acridin-9-yl) amino] propionate free base. May also refer to S-303 in solution (dissolved S-303 2HCl).
SAG- M	SAG-Mannitol: an RBC additive solution
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SD	Standard deviation
SOC	System Organ Class (MedDRA)
TA-GVHD	Transfusion Associated Graft versus Host Disease
TBD	To be determined
TEAE	Treatment-Emergent Adverse Event
TR	Transfusion Reaction
TRALI	Transfusion Related Acute Lung Injury
TTI	Transfusion-Transmitted Infection
UADE	Unanticipated Adverse Device Effect
WBC	White Blood Cells
WNV	West Nile Virus
ZIKV	Zika Virus

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2 BACKGROUND INFORMATION

Blood transfusion is a critical supportive therapy for healthcare. Patients and physicians assume that, when required, blood transfusion will be available and safe. However, serious transfusion-transmitted infections (TTI) caused by viruses, bacteria and protozoa (Stramer 2009, MacLennan 2006); and fatal transfusion complications such as transfusion-associated graft-versus-host disease (TA-GVHD) still pose a threat to transfusion recipients (Kopolovic 2015).

Although the recent emergence of SARS-CoV-2/COVID-19 as a pandemic infectious disease has not been shown to be a major transfusion transmission risk, the occasional demonstration of patient viremia and its propensity to manifest as an asymptomatic disease that would not prevent blood donation, suggests that it remains a risk that cannot be ruled out (Katz 2020). Nevertheless, SARS-CoV-2/COVID-19 has raised awareness of the need for protecting the future blood supply from similar emerging pathogens that may be efficiently transmitted by transfusion.

Currently, prevention of TTI includes pre-donation evaluation and selection of low-risk donors, followed by serologic and/or nucleic acid testing for selected known infectious pathogens.

Although the advent of testing has greatly reduced TTI from blood products, particularly viral disease, pathogens may still contaminate the blood supply because emerging infections are not predictable and may contaminate the blood supply for a period of time before discovery. There are limits to the level of sensitivity achievable with testing (Kleinman 2009, Kleinman 2015); FDA approved tests are not available for many of agents known to contaminate blood components; and finally, bacterial contamination is a major cause of blood product contamination despite implementation of early culture for platelet components but not for RBC components (Jacobs et al 2011, Corash 2011; Wenke 2010; Hong et al 2015).

Importantly, bacterial screening is applied only to platelet components even though products from the same donors may be used for manufacturing of RBC and plasma (Kleinman 2015).

Irradiation can effectively prevent TA-GVHD in transfusion recipients. However, current guidelines for blood irradiation fail to identify approximately half of the patients at risk for TA-GVHD, leading to substantial morbidity and mortality (Kopolovic 2015). Moreover, irradiation adversely affects post-transfusion RBC recovery (Dumont 2008) and is associated with high extracellular potassium levels.

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To proactively address the risk of TTIs and TA-GVHD, Cerus has developed pathogen and leukocyte inactivation technology systems (INTERCEPT Blood System™) for platelet and plasma components and is currently developing a system for red blood cell concentrates (RBCs). These systems use nucleic acid-targeted compounds that intercalate into and upon activation, covalently bind to nucleic acids of viruses, bacteria, parasites and leukocytes that may contaminate blood components, and form irreversible adducts and crosslinks, thus preventing replication and TTI. This process does not depend on or generate reactive oxygen species (ROS) which can damage cells and proteins. RBCs do not require nucleic acid for therapeutic function and thus, retain therapeutic efficacy after pathogen inactivation treatment. Furthermore, INTERCEPT treated RBC components should not require irradiation because the treatment process inactivates donor white blood cells with a high safety margin.

The INTERCEPT Blood System for RBCs inactivates a variety of bacteria, viruses and protozoa. The organisms evaluated to date include examples representing a range of different characteristics, such as enveloped (HIV and DHBV) and non-enveloped (Bluetongue virus), RNA genome (HIV and BVDV) and DNA genome (DHBV), and single stranded (HIV) and double stranded (DHBV) genomes. The bacteria evaluated represent Gram negative bacilli (*Yersinia sp., Serratia sp., E. coli, Salmonella sp.* and *Pseudomonas sp.*) and Gram-positive cocci (*S. epidermidis and S. aureus*) that are especially significant for RBC transfusion. The protozoan parasites evaluated to date are *Plasmodium falciparum* and *Babesia microti*. IBS RBCs have demonstrated adequate viability for transfusion (Cancelas et al. 2017), and a recently completed Phase 3 clinical studies conducted in Europe in cardiovascular surgery (Brixner et al. 2018) and thalassemia (Aydinok et al. 2019) patients have demonstrated that RBCs possess characteristics comparable to untreated RBCs, with a comparable safety profile (Rico et al. 2015). Cerus will be submitting these data in support of CE Mark registration.

Recently three vector borne arboviruses (Dengue [DENV], Chikungunya [CHIKV], and Zika [ZIKV] viruses) with potential for transfusion- transmission have emerged in several areas of the world (Roth et al. 2014). The latter is a prime example of an emergent virus with major implications for blood safety and availability (Lanteri et al. 2016) and re-emphasizes the value of a proactive approach to safeguard the blood supply. Given the proven potential to be transmitted by transfusion (Barjas-Castro et al. 2016, Motta et al. 2016) and its association with deleterious outcomes such as microcephaly (Mlakar et al. 2016; Tang et al. 2016) and Guillain-Barre syndrome (Cao-Lormeau et al. 2016), FDA issued a guidance recommending the cessation or

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additional of blood collections in areas with active transmission of ZIKV, such as Puerto Rico; or the use of an approved pathogen reduction device for plasma and for platelets (FDA 2016, Kuehnert & Epstein 2016). The INTERCEPT Blood System for platelets is the only pathogen reduction system currently approved by FDA for platelets, while Octaplas™ and the INTERCEPT Blood System are both approved for plasma. While there is no FDA approved pathogen reduction system yet for RBCs, the INTERCEPT Blood System for RBC has been shown to inactivate arboviruses such as DENV, CHIKV and ZIKV (> 4 $\log_{10}$).

The present study has the following aims: 1) evaluate the safety and efficacy of the INTERCEPT Blood System for RBCs in patients who require RBC transfusion support, 2) provide early access to the INTERCEPT Blood System for RBCs in regions where a substantial proportion of the population has been infected or is at risk of emerging transfusion transmitted infections, and 3) protect the blood supply and support self-sufficiency in these regions.

2.1 S-303 Name and Description of the Investigational Product

Please refer to the Investigators Brochure for a full description. Details are summarized here.

The investigational device is the INTERCEPT Blood System for Red Blood Cells. The pathogen reduction process begins with a unit of RBCs derived from whole blood that is separated according to local regulations and standard operating procedures at the Blood Centers. RBCs are suspended in additive solution-5 (AS-5) (or SAG-M at non-US sites). Leukocyte-reduction of whole blood or RBCs will be performed per manufacturer's instructions. The INTERCEPT Blood System process is performed on a single unit of leukocyte-depleted RBC in AS-5 (or SAG-M at non-US sites). For a detailed description of the investigational product, please refer to the Investigator's Brochure.

2.2 Summary of Nonclinical and Clinical Studies

Please refer to the Investigators Brochure for a full description. Details are summarized here.

The INTERCEPT treatment process uses amustaline and glutathione (GSH) together with a processing solution in a single-use disposable set and results in pathogen and leukocyte inactivated RBCs in SAG-M additive solution. Cerus' pre-clinical and clinical development program has determined amustaline/GSH efficacy for pathogen inactivation and safety profiles with regard to systemic toxicity, genotoxicity, and

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carcinogenicity in accordance with International Council on Harmonization (ICH) standards for development of pharmaceuticals. These data are presented in detail in the Investigator's Brochure.

2.2.1 S-303 Safety

No physiologically relevant toxicity using IBS RBCs at doses higher than planned for this trial was observed in pre-clinical studies (North et al. 2011). Additional information about the toxicological evaluations of the treatment system is provided in detail in the Investigator's Brochure.

2.2.2 Immunogenicity

The mechanism of action of amustaline can also lead to reactions with macromolecules other than nucleic acids in the RBC components, such as constituents of the red cell membrane. In early studies of the pathogen inactivation process for RBCs (previously referred to as "first generation process", in the current IB referred to as "original process") there was evidence of antibody formation directed against INTERCEPT RBCs (also referred to as S-303-specific RBC antibodies) in two patients participating in a chronic RBC transfusion study. In order to minimize these non-specific and unwanted reactions with RBC surface molecules, an increased level of the quencher, glutathione (GSH), has been included in the current, pathogen inactivation process (referred to as "Current process"). Additional information regarding the potential for immunogenicity, and the studies that have been conducted, is provided in the Investigator's Brochure.

2.2.3 Clinical Studies

Four clinical studies have been completed with the current INTERCEPT Blood System for RBCs. The studies are summarized in **Table 2-1** below and additional detail is provided in the Investigator's Brochure.

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Table 2-1 Summary of Clinical Studies with Second Generation INTERCEPT Blood System for RBCs

Study ID	Number of Study Centers	Design	Study & Ctrl Drugs (Dose, route & regimen)	Study Objective	# subjs (entered, completed)	Diagnosis	Primary Endpoint(s)	Main Findings
CLI00062 (RBC08001)	2	Randomized, single blinded, controlled, 2 period, cross-over	Single transfusion of 5- 15 mL of ^{51}Cr-labeled Test (S-303) or Control RBCs (35-day storage), intravenous	Recovery and life span of IBS treated autologous RBCs; safety and tolerability	26/26	Healthy adult patients	24-hour recovery and life span of 35-day old autologous RBCs	IBS-treated RBCs met FDA recommended criteria for 24-hour recovery with no significant difference between IBS-treated and control RBC Survival was significantly different between Test (32.8) and Control (39.5) but T50 of Test was within published reference range (days) No physiologically meaningful differences at end of storage between Test and Control RBC
CLI00070 (Brixner et al. 2018)	3	Randomized, controlled, double blinded, parallel	IBS treated or untreated RBC transfusions for up to 7 days starting @ day of surgery; dose and frequency per treating physician	In vitro characterization of IBS RBCs relative to EU criteria for RBC for transfusion obtain clinical data to support design of add'l studies to support registration of IBS for RBC	7 Randomized; 1 treated 25T, 26C)	Patients undergoing complex cardiac surgery with high likelihood of requiring RBC transfusion	Primary in vitro endpoint Hb content/unit Primary clinical endpoint = safety Exploratory endpoints indicative of tissue oxygenation include renal or hepatic insufficiency and 6MWT	IBS RBC demonstrated equivalence to untreated RBC regarding hemoglobin content; the proportion of IBS RBCs satisfying the EDQM guidelines was higher than for conventional RBCs. The incidence of renal insufficiency was 15.7% (Test 5, Control 3, p=0.41). The incidence of hepatic insufficiency was 2% (Test 1, Control 0, p=0.37). There was no statistical difference between Test and Control groups for the assessments of the 6MWT at the time of first ambulation post-surgery and at day 13 or discharge. No statistical differences in the overall incidence of AE rates, or in possibly related AEs between Test and Control, with similar distribution of SAE between groups. The events observed were those expected in this population.
CLI00073 (Cancelas et al 2017)	2	Single-blinded, randomized crossover;	Single transfusion 10-30 mL of ^{51}Cr-labeled Test (S-303) or Control RBCs (35-day storage), intravenous	Compare survival and recovery of autologous S-303 RBCs to conventional RBCs	42 enrolled/ 26 completed	Healthy patients	24 hour post-infusion dual label recovery of autologous RBCs stored for 35 days	The 24-hour post-transfusion recovery (both dual- and single-label) of autologous IBS RBCs following infusion after 35-days of storage met all the FDA criteria for the evaluation of RBC products. No immunologic reactivity developed to Test RBC.

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Study ID	Number of Study Centers	Design	Study & Ctrl Drugs (Dose, route & regimen)	Study Objective	# subjs (entered, completed)	Diagnosis	Primary Endpoint(s)	Main Findings
CLI00076 (Aydinok et al. 2019)	3	Randomized, controlled, double blinded, two-period, crossover, non-inferiority	Six transfusion episodes of Test (INTERCEPT) or Control RBC; each treatment period to include 2 wash-in and 4 investigation episodes; maintain the same target hemoglobin level specified by treating physician	Evaluate the efficacy and safety of INTERCEPT RBCs in subjects who require chronic transfusion support due to thalassemia major	Safety population was 81 subjects; Intent to Treat 80 subjects and Per Protocol 75 subjects.	Transfusion-dependent Thalassemia	Hemoglobin consumption during each efficacy evaluation period is measured as the hemoglobin mass transfused per subject adjusted for episode-specific body weight and duration (adjusted Hgb consumption units are Hgb g/kg body weight/day). Incidence of a treatment-emergent antibody with confirmed specificity to INTERCEPT treated RBCs associated with clinically significant hemolysis Incidence of adverse events	Mean hemoglobin consumption (g/kg/day) with INTERCEPT RBCC was not inferior ($p < 0.001$) to conventional RBCC (0.113±0.04 versus 0.111±.04, p=0.373) by intent to treat (80 subjects) or per protocol (71 subjects) (0.112±0.04 versus 0.110±.03, p=0.162) analysis. Similar results were found for asplenic (ITT: 0.91±0.03 versus 0.92±.03, p=0. 613) and eusplenic (ITT: 0.135±0.03 versus 0.130±.03, p=0.222) subjects. No antibodies specific to INTERCEPT RBCC were detected; and there were no substantial differences in transfusion reactions, adverse events or serious adverse events recorded.

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2.3 Summary of Potential Risks

The potential risks of this study include those adverse reactions that are recognized to occur following any transfusion of RBC components and could be anticipated to occur with either conventional or INTERCEPT-treated components including, but not limited to, delayed serologic transfusion reactions (DSTRs), acute hemolytic transfusion reactions (AHTRs), delayed hemolytic transfusion reactions (DHTRs), febrile non-hemolytic transfusion reactions (FNHTRs), allergic (urticarial) reactions, anaphylaxis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion related sepsis (TRS, transfer of an infectious agent via transfusion/transfusion transmitted infection (TTI), respectively, transfusion associated graft-vs-host disease (TA-GVHD), and allo-immunization to RBC and HLA antigens.

The development of antibodies to S-303 treated RBCs, or to neoantigens formed as a result of S-303 binding to red cells, could occur as a result of transfusion with IBS RBCs. Acridine-specific antibodies were observed in early and current ongoing blinded studies (as described in the Investigator's Brochure) and many could be neutralized with acridine in solution, thereby defining specificity for this moiety. The occurrence of these antibodies was not associated with any clinical events or observations.

A screening study was performed to evaluate the prevalence of natural antibodies with specificity for INTERCEPT RBCs (SUD 00742). Five plasma samples from 998 subjects requiring chronic transfusion support for anemia and 12 plasma samples from 10,721 hospital subjects demonstrated low titer cross-reactions with INTERCEPT RBCs. The cumulative prevalence of cross-reactive antibodies to INTERCEPT RBCs was 0.15%. Each of the antibodies identified was characterized and none were found to be IgG_1 or IgG_3 subclass, the antibody subclasses most associated with physiologic hemolytic activity. The majority demonstrated specificity for acridine.

Several instances of treatment emergent antibodies with specificity for INTERCEPT RBCs were reported during the ongoing Phase III clinical investigations. In each event, the antibodies were shown to be non-clinically significant without evidence of patient harm. These studies remain blinded, and it is not known whether the patients received Test or Control RBCs. Natural antibodies to INTERCEPT RBCs are expected to occur in ongoing clinical trials.

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Risk mitigation is in place to protect patients and further evaluate clinical significance. In this study, patients are screened for antibodies to IBS RBCs every time a routine IAT antibody screen is performed during the study transfusion period. Subjects with natural cross-reactive antibodies are screen failed. Subjects are regularly screened during the study including approximately 75 days after the last study RBC transfusion in all ongoing clinical trials. Patients with treatment emergent antibodies to IBS RBCs are withdrawn from receiving study RBC transfusions and are fully evaluated for evidence of hemolysis. Stopping rules are in place related to the occurrence of delayed serological and hemolytic TRs associated with treatment emergent antibodies to INTERCEPT RBCs.

The risk of bacterial contamination is considered to be negligible with IBS RBC components and, although it has not been measured directly, is expected to be less than the risk of bacterial contamination with conventional RBC components, thus providing a potential benefit of receiving INTERCEPT-treated components.

Finally, human error, clerical error, and transfusion of RBC to the wrong patient remain risks of transfusion.

2.4 Description of and Rationale for Treatment

Recent outbreaks of arboviral disease in the Americas have included large ZIKA, dengue and chikungunya virus outbreaks. In addition to collecting further information on the safety and efficacy of IBS RBCs, a major objective of this study is to provide access to locally collected RBC and ensure local self-sufficiency by using the INTERCEPT Blood System for Red Blood Cells Pathogen Reduction System in regions where a substantial proportion of the population has been infected or is at risk of infection by emerging infectious diseases.

For example, according to the FDA's "Guidance for Industry: Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion Transmission of Zika Virus (February 2016)" (referred to hereafter as "FDA ZIKV Guidance"), the ZIKV reached the region of the Americas in early 2015 with local transmission first reported in Brazil, and as of February 10, 2016, there are 30 countries and territories worldwide with active local transmission of the virus. Two instances of possible transfusion-transmission have been described in media announcements in Campinas, Brazil (ECDC; Outbreak News Today; Barjas-Castro, ML et al. 2016). In French Polynesia, 2.8% of samples from asymptomatic blood donors contained detectable ZIKV RNA during the outbreak in French Polynesia in 2013-2014, indicating the likelihood of transmission by blood transfusion (Musso et al. 2014).

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According to the FDA ZIKV guidance referenced above, the risk of transmission of ZIKV by blood transfusion is considered likely based on the following evidence:

a) Two possible cases of transfusion-transmission in Campinas, Brazil (Barjas-Castro, ML et al. 2016, Motta et al. 2016).

b) There have been documented transfusion-transmissions of other flaviviruses such as West Nile virus, dengue virus and Yellow Fever virus, all of which have been shown to produce detectable viremia (the presence of virus in the blood) during asymptomatic and symptomatic infections.

c) ZIKV infection produces viremia with up to 8.1×10^6 genomic copies/mL corresponding to approximately 1000 times less in vitro infectivity (Aubry et al 2015, Besnard et al 2014, Gourinat et al 2015), that may last up to (and possibly beyond) 14 days, with varying reports of viremia from 2 days before to 11 days after onset of symptoms; ZIKV RNA persists for up to 2 months in the RBC compartment (Lustig et al. 2016).

d) The pre-symptomatic period for ZIKV infection varies (if symptoms develop) from 3 to 12 days, during which viremia may occur.

e) An estimated 80% of ZIKV infections remain asymptomatic.

f) Perinatal transmission of ZIKV, most likely by trans-placental transmission or during delivery, has been reported.

g) Blood donations positive for ZIKV viral RNA by nucleic acid testing (NAT) were detected in 2.8% of donors during the French Polynesia outbreak in 2013-2014.

The IBS System has been demonstrated to effectively inactivate a spectrum of viruses, including flaviviruses, such as dengue and West Nile virus, in platelets and in plasma, and bovine viral diarrhea virus (BVDV) and CHIKV in RBCs; BVDV is a model for human HCV and other flaviviruses, such as WNV, dengue virus and ZIKV. A recent publication showed that the IBS pathogen reduction technology for platelets and plasma using amotosalen and UVA can effectively inactivate ZIKV infectivity in plasma (Aubry et al. 2016).

Thus, expeditious safety assessment and early access to RBC pathogen inactivation technology is critical in areas experiencing or expected to experience substantial rates of infections due to emerging infections such as ZIKV that may be transfusion transmitted.

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2.4.1 Rationale for Efficacy Measures

2.4.1.1 Hemoglobin Increment in Non-bleeding Patients

Although the study will enroll both bleeding and non-bleeding patients, the primary efficacy endpoint, adjusted hemoglobin increment, will be assessed only in non-bleeding patients at baseline in both the 28-day acute and 6-month extension periods. Patients with sickle cell anemia, thalassemia, MDS or other medical conditions with bone marrow failure will be invited to enroll in the 6-month extension period.

We aim to evaluate and compare Hb increment in patients undergoing RBC transfusions with IBS and conventional RBC, to explore the influence of pathogen reduction treatment, the patients' underlying condition and hemoglobin dose on Hb increment as a measure of RBC efficacy.

Anticipated surgical bleeding and planned blood loss/replacement through red cell exchange at baseline are considered "active bleeding (Grade ≥3)" by definition. Both are planned situations that require RBC transfusion to replace blood loss.

An RBC transfusion episode is defined to include consecutive RBC units transfused until the next post transfusion Hb determination, with ≤12 hours between transfusions (from the end of a prior component transfused to the start of a subsequent component transfused).

Adjusted hemoglobin increment is defined as the difference between the pre-transfusion episode and the post transfusion episode hemoglobin values (taken within 15 minutes to 24 hours of the end of a transfusion episode, before the next transfusion) divided by the total hemoglobin content transfused, averaged over one or more transfusion episodes in patients without active bleeding at baseline (active bleeding is defined as WHO Grade 3 or 4 bleeding).

Hemoglobin increment in non-bleeding patients represents the most readily available and commonly used clinical assessment of transfusion efficacy. It is a measure of *in vivo* recovery of transfused RBCs. Based on long-standing assumptions, each RBC unit was thought to increase recipient hemoglobin by ~1 g/dL. Recent retrospective observational studies have demonstrated an unexpectedly large variation in hemoglobin increment per RBC unit transfused and identified several influences on measured Hb increment as the outcome of RBC transfusion, including donor, recipient, and product characteristics (Roubinian 2019). Part of this variance is likely due to the large variation in hemoglobin content of RBC components (Aydinok 2019).

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2.4.1.2 Hemoglobin Consumption in Non-bleeding, Chronically Transfused Patients

The secondary efficacy measure is the adjusted hemoglobin consumption, defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (g/kg/day), in sickle cell anemia, thalassemia, MDS or other bone marrow failure patients without active bleeding at baseline. The analysis will be conducted only in non-bleeding patients who participate in both of the initial 28-day acute and 6-month extension transfusion periods and will utilize integrated data from both periods, as hemoglobin consumption is best assessed over prolonged time periods of time.

Hemoglobin consumption per body weight and duration of support to correct anemia provides an integrated direct measure of *in vivo* RBC component efficacy because it indicates the clinical response to transfusion and is dependent on both RBC recovery and survival in vivo. Clinicians order RBC components based on varying transfusion thresholds dependent on individual patient clinical conditions. Analysis of utilization with consideration of important covariates (e.g., indication for transfusion, age, race, sex) will be informative about efficacy over a wide range of RBC component transfusion indications. Hemoglobin consumption in non-bleeding patients is a measure of the iron burden of transfusion. Increased consumption might be expected if IBS RBC have reduced *in vivo* recovery and/or survival compared to conventional RBC. It is most relevant to patients receiving regular, repeated RBC transfusions for chronic anemia who are prone to develop iron overload over time, requiring iron chelation treatment. Radio-labelling studies in normal volunteers have demonstrated that IBS RBCs have acceptable in vivo recovery and survival and meet FDA requirements with regards to these parameters (Cancelas et al. 2017). Adjusted hemoglobin consumption of IBS RBC compared with conventional RBCs will be assessed as a secondary endpoint only in patients who participate in both initial and extension periods with a non-inferiority margin of 15% representing a potential increase in iron load that is within the capacity of existing iron chelation therapies.

2.4.1.3 HbA Clearance in Sickle Cell Disease Patients Undergoing Regular Repeated Red Cell Exchange

The 28-day +6-month extension period will include a subset of SCD patients undergoing repeated RCE. Within this subgroup, the efficacy assessment is a comparison of the mean of the difference in the HbA clearance rate (g/dL/day) averaged over three RCE episodes in subjects receiving Test RBCs (INTERCEPT RBCs) versus those receiving Control RBCs (conventional RBCs).

Preliminary analysis of patients undergoing regular RCE at University College

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London revealed a mean inter-RCE interval of 39.3 days (min 26.1 and max 54.8 days). HbA % (19 patients) and concentration (11 patients) were assessed immediately before and after each RCE to estimate potential clearance rates of conventional RBC. The mean HbA clearance was 0.66 (SD 0.13) percent/day and in 11 patients where data were available, 0.082 (SD 0.022) g/dL of HbA per day. The relatively large variation (assessed as the standard deviation) is ascribed to variation in the RCE procedures performed and, in the subject's, medical condition over time (e.g., infections and sickle cell crises). Analysis of HbA clearance based on the average of three consecutive RCE procedures reduced the coefficient of variation (CV) to a mean clearance of 0.66 (SD 0.06) percent per day. The CV was not further reduced by analyzing the average of 4 or 5 consecutive RCE procedures, suggesting that 3 RCE procedures in each arm was an optimum study design.

Similar variability in HbA clearance was described by Yee et al. and Sagiv et al (Yee 2019, Sagiv et al. 2019). The rate of decline in HbA between transfusion events was strongly associated with increased HbS, increased reticulocyte count, and lower total Hb at the end of the transfusion cycle, demonstrating the relevance of transfusion clearance to the suppression of erythropoiesis and thus to hematologic and clinical outcomes. Greater declines in HbA were associated with past RBC alloimmunization and splenomegaly, while less rapid clearance of HbA was found in those with past splenectomy. Additionally, broad intra-patient variability in HbA decline with different transfusion episodes suggested the influence of blood donor and unit-specific characteristics on transfusion survival. Glucose 6-phosphate dehydrogenase (G6PD) deficiency, found in 9% of the donor units (Sagiv et al. 2019), was associated with more rapid HbA decline and increased erythropoiesis. G6PD is the key enzyme in the metabolic pathway to protect RBC from reactive oxygen species and organic peroxides that contribute to RBC damage and hemolysis. These studies estimated the post RCE HbA levels in a substantial portion of their data due to missing data points, likely contributing to the described high levels of variability in HbA clearance rates.

Taken together, these data demonstrate equipoise whether post-RCE assessments of HbA percentage and concentrations at 15 minutes to 4 hours under the controlled conditions of a clinical study will further reduce variation.

To minimize the effects of inter-patient and intra-patient variation in HbA clearance rates:

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- Patients will be on an established RBC transfusion regimen during the clinical trial and will be transfused to maintain a hemoglobin S level of approximately 50% or less.
- Pre transfusion and post- RCE measures of HbA concentrations will minimize errors associated with estimated data
- The HbA clearance rate will be calculated using the average of the three RCE transfusion episodes.

2.5 Conduct of the Trial

This study will be conducted in accordance with Good Clinical Practice (GCP) according to the International Conference on Harmonization (ICH) guidelines, and local ethical and legal requirements that are consistent with the Declaration of Helsinki.

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3 STUDY OBJECTIVES

The objective of the randomized, blinded, controlled stage of the study is to evaluate the safety and efficacy of the INTERCEPT Blood System for Red Blood Cells in comparison to conventional RBCs in patients who require RBC transfusion support.

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4 INVESTIGATIONAL PLAN

4.1 Endpoints

Primary:

- The primary efficacy endpoint evaluated in all non-bleeding patients at baseline, excluding RCE patients, is the adjusted hemoglobin increment, defined as the difference between the pre-transfusion episode and the post-transfusion episode hemoglobin values (taken within 15 minutes to 24 hours of the end of a transfusion episode, before the next transfusion) divided by the total hemoglobin content transfused, averaged over one or more transfusion episodes in patients without active bleeding at baseline (active bleeding is defined as WHO Grade 3 or 4 bleeding).
- The primary safety endpoints evaluated in all patients are:
    - The proportion of patients with any treatment-emergent adverse events possibly, probably, or definitely related to study RBC transfusion through 28 days after the last study transfusion.
    - The proportion of patients with treatment-emergent antibodies with confirmed specificity to IBS RBCs.

Secondary endpoints include:

- Excluding RCE patients, the secondary endpoint is the adjusted hemoglobin consumption, defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (g/kg/day), in patients without active bleeding at baseline.
- For SCD patients enrolled into the 28-day + 6-month extension for three RCE procedures, the endpoint will be HbA clearance.
- Safety (evaluated in all patients):
    - Treatment-emergent AEs for 28 days after last study transfusion;
    - Transfusion reactions related to study RBCs (test or control) (as defined by the CDC NHSN Hemovigilance Module protocol) for 28 days after last study transfusion;
    - Treatment-emergent immunization to RBC allo-antigens; and
    - All-cause mortality through 28 days after last study transfusion.

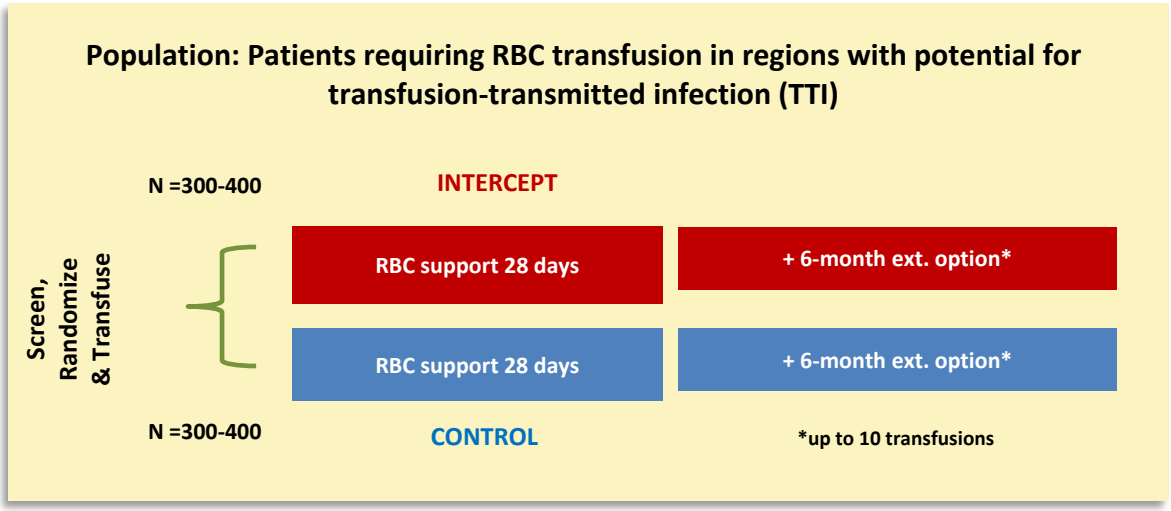
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- Safety (SCD patients enrolled into the 28-day + 6-month extension for three RCE procedures):
  - Proportion of subjects with AESI (see definition in **Section 7.3.1.2**). through 28 days after the last study transfusion, or until the next routine RCE procedure if less than 28 days;
  - S-300 and Glutathione (GSH) plasma levels before and 15 minutes to 4 hrs after RCE.

4.2 Study Design

The study is a multicenter, randomized, double-blinded, active controlled, parallel-design clinical trial, with an extension option to evaluate for patients requiring repeated transfusion for chronic anemia or for repeated RCE procedures (**Figure 4.1**),

Figure 4.1 Study Scheme



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4.3 Randomization and Blinding

Patients will be approached, consented, screened for eligibility, and randomized to receive either Test or Control RBCs in one of the three arms of the study at the beginning of the study:

- Bleeding or non-bleeding patients at baseline may be enrolled into the 28-day transfusion period.
- Non-bleeding patients at baseline with chronic anemia requiring repeated simple transfusion may be enrolled into the 28-day +6-month extension period.
- SCD on a regular repeated RCE program at baseline may be enrolled into 28-day +6-month extension period to receive 3 consecutive RCE procedures.

Potentially eligible patients will be consented and begin screening in the study to be considered for randomization. Subjects < 18 years will be assented, and parental consent obtained. Subjects electing to participate in the 28-day +6-month extension option should be consented and enrolled at the time of initial consent. An Interactive Web Response System (IWRS) will be used for electronic randomization of eligible patients. At the end of screening and prior to the first study RBC transfusion, the patient's eligibility status will be entered into the electronic data capture system. If eligible, the patient will be randomized to receive either IBS RBCs or conventional RBCs in a 1:1 ratio. Randomization will be stratified by site, baseline bleeding status (indication for RBC transfusion due to active bleeding or for anemia without active bleeding), patients' participation in the optional extension period (yes/no) and patients' need for RCE. Active bleeding will be defined as Grade 3 or 4 bleeding of the expanded WHO bleeding scale (**APPENDIX 5**, Miller 1981 & McCullough 2004). Anticipated surgical bleeding and planned blood loss/replacement through RCE at baseline should be included as active bleeding (Grade ≥3) by definition.

Randomized patients who do not receive any study RBC transfusions through 28 days post-randomization will be discontinued from the study and replaced. Additional data will not be collected for these patients, nor will they be part of the data analysis. These subjects may be reassessed for eligibility and re-enrollment after withdrawal.

Only appropriate blood bank and transfusion service staff will be able to access the treatment arm assignment. Study RBC component labels will be indistinguishable for Test and Control products.

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In order to protect the blind, on the day of planned transfusion, the final product (test and control) may be transferred into an FDA approved RBC storage container (Fenwal™ Transfer Pack™ Container – 600 mL, product code 4R2023) using a sterile docking technique. Blood transferred into an ancillary container should be stored at 1°C to 6°C and transfused within 7 calendar days of transfer.

Clinical staff and others caring for participating patients, as well as the sponsor (and delegates) will be blinded to treatment assignment. Unblinded delegates will monitor the production of the RBC components at designated blood centers and distribution at hospital transfusion centers.

4.4 Treatment

Patients may volunteer to participate in the:

- Acute study only (28-day treatment period)
    - Bleeding or non-bleeding patients (including RCE)
- Or the 28-day acute plus the 6-month extension period option
    - Non-bleeding sickle cell disease, thalassemia, MDS, aplastic anemia, chemotherapy bone marrow failure patients requiring repeated simple transfusions
    - Sickle cell disease patients on regular, repeated RCE

Repeated Simple Transfusion Arm

Eligible subjects will be randomized to receive either IBS RBCs (Test) or conventional RBCs (Control) for up to 28 days or death, whichever is first in the initial acute transfusion period, and for an additional 6-months or up to 10 transfusion episodes, whichever occurs first. Subjects will maintain the same randomization if the subject is entered into the extension transfusion period option. During these periods, patients will receive as many study RBCs as deemed appropriate by the treating physician for up to 10 transfusion episodes.

RCE Arm

Eligible subjects will be randomized to receive 3 consecutive RCE using either INTERCEPT RBCs (Test) or conventional RBCs (Control) for 28 days plus 6-months.

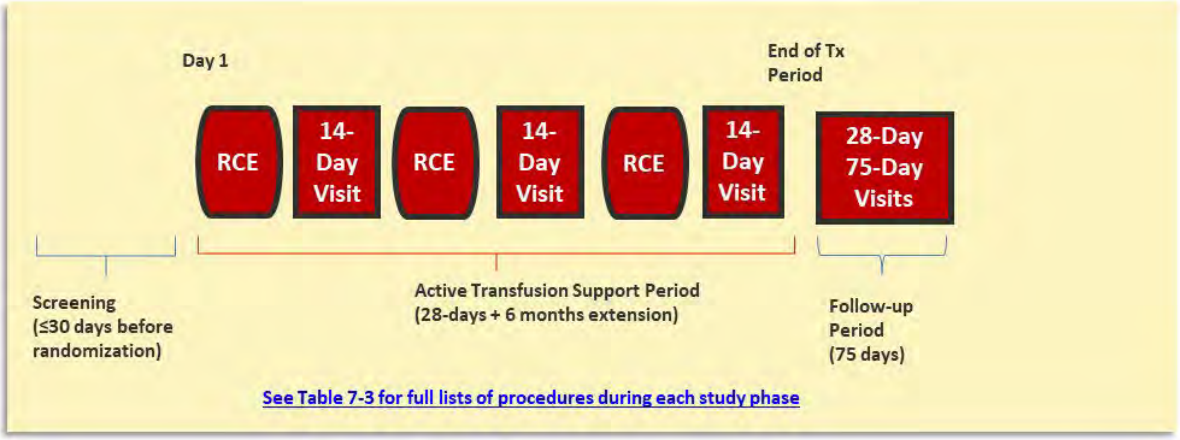
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Study RBC components will be ordered and administered to study patients by their treating physicians, also according to the local standards of care. A confirmed negative crossmatch (electronic or IAT) with IBS RBCs is required for every study transfusion. Type and Screen (IAT) for S-303 antibodies must be performed before the first transfusion and at every time point a Type/Rh and Screen (IAT) is ordered during the 28-day and the 6-month extension period. Following the study treatment period (28 days or 28 days plus additional 6 months extension, as applicable) patients will receive conventional RBC components if needed, as indicated by their treating physician. In all patients, anesthesia, surgical, and other procedures will be performed according to the local standards of the institution.

Figure 4.2 Study Scheme – Study RBC Transfusions



Figure 4.3 Study Scheme – Study RCE Transfusions



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4.4.1 Investigational Product

4.4.1.1 Donation and Preparation of Study RBCs

All blood donors will be screened and qualified according to applicable local regulations and standard operating procedures at each Blood Center. The whole blood will be collected in anticoagulant Citrate Phosphate Dextrose (CPD) solution using the Imuflex® WB-RP (code BB*WGQ506A2) or WB-SP (code BB*LQG506A6) Blood Bag System (Terumo, Japan) in the US, or the standard whole blood collection procedure in routine use in non-US sites. On the day of collection, the whole blood will be processed into RBCs suspended in AS-5 (or SAG-M in non-US sites). Leukocyte-reduction, by filtration, will be performed in whole blood or RBCs in additive solution and RBCs will be stored at 1°C to 6°C.

4.4.1.2 Processing of Test Product RBC Components

The test device is the INTERCEPT Blood System for RBC and is described above in the Investigators Brochure. The test product is allogeneic INTERCEPT-treated RBC components (IBS RBCs) stored in SAG-M at 1°C to 6°C (or 2ºC to 6ºC at non-US sites) for up to 35 days post-donation and administered intravenously. AS-5 (or SAG-M at non-US sites) RBCs meeting the collection specifications will be treated using the INTERCEPT Blood System for RBCs within 24 hours after whole blood collection.

Test RBC components will be released to clinical inventory after review of the batch production record associated with the INTERCEPT treatment process. Test components may be irradiated, if indicated by the treating physician.

4.4.1.3 Processing of Control (reference) RBC Components

The Control transfusion component is whole blood derived conventional leukocyte reduced RBC suspended in suspended in an FDA approved additive solution (e.g., AS-1, AS-3 or AS-5 (or SAG-M at non-US sites) and stored at 1°C to 6°C (or 2ºC to 6ºC at non-US sites) for up to 35 days post-donation and administered intravenously. The Control RBC components will be labeled in a manner to maintain blinding. Control products may be irradiated as required. Control RBC components will be released to clinical inventory after review of the batch production record associated with the trial.

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4.4.1.4 Evaluation of Red Blood Cells at the Blood Centers

Samples will be collected from the Control and input Test RBC components and from the Test RBC component post INTERCEPT processing. To preserve the quality of the RBC components, samples will be obtained using standard blood bank processing techniques, including sterile tubing connection devices and tube sealers to minimize hemoglobin loss and maintain a functionally closed system. Samples acquired from the RBC units will be used for determination of the parameters outlined in Table 4-1.

Table 4-1 Evaluations for Test and Control RBC Components

	Test	Control
Volume (mL)[a]	Input Post IBS	Prior to release [b]
Hemoglobin Concentration (g/dL)	Input Post IBS	Prior to release [b]
Hematocrit (%)	Input	Not applicable
Hemoglobin Content (g)[a]	Input Post IBS	Prior to release [b]

[a] Determined from post-sampling weight
[b] Prior to release into clinical inventory (Day 0-4)

4.5 Accountability of Study Product

The Investigational Product includes both the INTERCEPT Blood System for RBCs, a medical device used to prepare pathogen and leukocyte inactivated RBC components for transfusion, and the investigational biological product, INTERCEPT-treated RBCs (INTERCEPT RBCs).

The investigational device accountability will be verified by the unblinded study monitors throughout the duration of study. They will ensure that the device components are under control at all times inclusive of shipment, storage, usage, and disposition.

The investigational biologic product will be produced by each study Blood Center according to the Study RBC Processing Procedures and accountability will be tracked using the Blood Center's electronic data management system.

Both Test and Control study RBC components are for the sole use of study participants. Control components may not be crossed back into general inventory at a blood center or clinical site after they have been labelled and released into study inventory. The disposition of all components prepared for the study (transfused, discarded or expired) will be recorded. The investigational biologic product

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accountability will be verified by the study monitors throughout the duration of study.

4.5.1 Source Data

The patients' medical records are considered the source data; the study data will be recorded on electronic case report forms (eCRF). Batch production records and data reports from the blood center's EDMS may be considered source data for processing study RBC components.

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5 SELECTION AND WITHDRAWAL OF PATIENTS

5.1 Patient Inclusion Criteria

The following conditions must be met before a patient may be randomized in the study.

For all enrolled patients:

1. Age ≥4 years
2. Patients who require or expected to require a transfusion of RBC component(s), including red cell exchange transfusion
3. Signed and dated informed consent form
4. Female patients of child-bearing potential must:
    - Have negative serum or urine pregnancy tests performed at the Screening visit within 30 days of randomization to rule out pregnancy, and
    - Agree to use at least one medically accepted method of birth control that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner for the duration of study participation and for an additional 28 days.

For 28-day +6-month extension study in repeated simple transfusion subjects:

5. Non-bleeding subjects at baseline who meet all other inclusion and exclusion criteria and who require repeated simple RBC transfusion for congenital or acquired chronic anemia (e.g., sickle anemia, thalassemia, other hemoglobinopathies, myelodysplastic syndrome, aplastic anemia, chemotherapy or stem cell transplant etc.) will be eligible to participate in an optional extension period for up to 6 months or up to 10 transfusion episodes, whichever occurs first, after completion of the initial 28-day acute transfusion period.

For 28-day +6-month extension study in SCD patients requiring regular repeated RCE:

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6. Sickle cell disease patients on a regular RCE program will be eligible to participate in the optional extension period for up to 6 months for a total of three consecutive study RCE procedures, after completion of the initial 28-day acute transfusion period, if they meet the following criteria.
    - Diagnosis of sickle cell disease, either HbSS, HbSC or HbSB0 thalassemia, confirmed by Hb electrophoresis, deoxyribonucleic acid (DNA) analysis or high-performance liquid chromatography (HPLC).
    - Currently participating in an automated RCE transfusion program (for at least 3 months prior to enrollment) with 3- to 8-week intervals between RCE transfusion episodes.

5.2 Patient Exclusion Criteria

Patients will be excluded from this study if they meet any of the following criteria:

1. Confirmed positive baseline serum/plasma antibody specific to IBS RBC as determined by INTERCEPT S-303 antibody screening panel prior to receiving their first study transfusion.
2. Pregnant or breast feeding.
3. Patients who require neonatal transfusions and intrauterine transfusions.
4. Pre-existing antibody to RBC antigens that may make the provision of compatible study RBC components difficult.
5. History of transfusion reactions requiring washed RBCs, volume reduced RBC, or RBCs with additive solution removed.
6. Patients with documented IgA deficiency or a history of severe allergic reactions to blood products.
7. In addition, patients will be excluded from the study if they meet the following criteria:
    - Presence of an RBC warm autoantibody with evidence of active hemolysis.
    - Positive DAT as defined below:
        - A polyspecific-DAT reaction strength > 2+, or
        - A polyspecific-DAT (any strength) in conjunction with pan-reactivity with a commercial IAT antibody screening panel that precludes the

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identification of underlying alloantibodies or indicates the presence of autoantibody.

8. Have received investigational products, including investigational blood products, pharmacologic agents, or imaging materials, within 28 days prior to randomization. Prior receipt of conventional blood products tested with an investigational NAT test is not considered ground for exclusion.

9. Patients presenting with or expected to have massive hemorrhage (≥10 RBC units within 24 hours) or expected to require massive transfusion protocols. Planned red cell exchange does not apply.

10. For SCD patients to be enrolled into the repeated RCE 28-day +6-month arm of the study:

- A history of acute chest syndrome in the last 6 months, or hyperhemolysis syndrome at any time.
- Clinical evidence of splenic hyperfunction or splenic enlargement: ≥18 cm in longitudinal diameter (diagnosed at the Investigator's discretion according to the data available with ultrasound data being preferable).
- Currently receiving chemotherapy for treatment of cancer. Hydroxyurea for sickle cell disease is acceptable if subject has been on stable therapy for 3 months and no changes to dosage are planned.
- Subject is in active treatment with renal dialysis.
- Any subject for whom a substantial change in the number of RBC components transfused is anticipated due to anticipated splenectomy, bone marrow transplant, surgery or other change in clinical status.
- Subject with known G6PD deficiency or requiring treatment with medications that are known to adversely affect RBC viability or bone marrow function.

5.3 Patient Withdrawal Criteria

Study patients are free to withdraw consent and discontinue/withdraw participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may be withdrawn at any time at the discretion of the Investigator if he/she feels it is in the patient's best interest.

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Patients may be withdrawn from the study treatment if they:

- Become pregnant.
- Are treated with a concurrent prescribed medication demonstrated to have caused hemolysis while on study.
- Are randomized in the study, but do not undergo a study RBC transfusion within 28 days of randomization. (Note: These patients that are randomized but not treated with study RBC components will not be included in the data analysis.) These subjects may be reassessed for eligibility and re-enrollment after withdrawal.
- Develop an IBS RBC specific Delayed Serological Transfusion Reaction with no evidence of hemolysis (see definition in **Section 7.3.1.6**).
- Antibody with confirmed or indeterminate IBS RBC specificity and require further treatment with RBC transfusions.
- Develop an antibody specific to IBS RBCs with clinically significant hemolysis (see definition in **Section 7.3.3.1**).
- Become allo-immunized to minor blood group antigens such that provision of compatible blood is not feasible, requiring the use of non- study transfusions.
- Experience a Grade 3 or higher allergic reaction to study RBC. According to the current CTCAE, a Grade 3 allergic reaction is prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), there is recurrence of symptoms following initial improvement; or hospitalization is indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates).

Upon early termination or withdrawal of patients who have received at least one study transfusion, the tests required on the Day 28 (*± 7 days*) and/or Day 75 (*± 15 days*) visits will be performed. If this is not possible then a physical examination, concomitant medications, AEs, standard laboratory tests, and other blood samples should be performed depending upon the study period in which the patient was withdrawn.

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6 TREATMENT OF PATIENTS

6.1 Treatment Plan

6.1.1 Screening/Recruitment (Up to 30 days prior to randomization)

Patients will be approached, consented, screened for eligibility, and randomized into one of the three arms of the study at the beginning of the study:

- Bleeding or non-bleeding patients at baseline may be enrolled into the 28-day acute transfusion period.
- Non-bleeding patients at baseline with chronic anemia requiring multiple repeated simple transfusions may be enrolled into the 28-day +6-month extension period.
- SCD on a regular repeated RCE program at baseline may be enrolled into 28-day +6-month extension period to receive 3 consecutive RCE procedures.

All potentially eligible patients at participating institutions will be approached for study consent (and assent, when appropriate) prior to their transfusion. Subjects <18 years of age will require subject assent and parental consent. For subjects eligible for enrollment into the six-month extension period, consent/assent for the extension period should be obtained at initial enrollment.

Patients who consent to the study will be assigned a study ID number and undergo screening.

Screening data collection and procedures will include: demographics (age, sex), vital signs, height, weight, indication for anticipated transfusion, type of scheduled surgery (if applicable), medical and surgical history, transfusion history, physical examination, comorbid conditions, concomitant medications, hematology panel (WBC, RBC, Hb, Hct, MCV, MCH, MCHC, MPV, RDW, PLT, Neut %, Mono%, Lymph%, Baso%, Eos%), blood type and Rh, IAT, blood chemistry panel (BUN, Creat, EGFR, NA, K, GU, Cl, CO_2, TP, ALB, ALKP, AST, ALT, LDH, CPK, TBIL, DBIL), coagulation panel (PT, INR, APTT, Fibrinogen), DAT, immune reactivity to IBS RBCs, and pregnancy test (when applicable). The pregnancy test (when applicable) must be performed 30 days prior to randomization.

If results from the Screening assessments listed in Table 7-1, Table 7-2 and 7-3 are available in the medical record within 30 days prior to randomization, those data may serve as the screening data and the assessments do not need to be repeated unless the subject has an RBC transfusion in the 30-day period.

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If an RBC transfusion occurs after determined eligibility but prior to randomization, the subject may be randomized and those Screening assessments listed in Table 7-1, Table 7-2 and 7-3 should be repeated prior to the first study transfusion.

For SCD patients on a regular RCE program, if available in the medical record, the pre- and post- RCE total Hemoglobin, HbA, HbS and HbF concentrations should be recorded for up to 6 months prior to the first study transfusion.

6.1.2 Transfusion Support Period (First study transfusion through Day 28 or Day 28 plus additional 6-months)

Patients will be randomized to receive IBS RBCs (Test) or conventional RBCs (Control), during the transfusion support period, or death, whichever is first (28-day acute transfusion support period or 28-day acute support period plus additional 6-months extension, as applicable). The day of first transfusion will be considered study Day 1 for defining the transfusion support period. All transfusions administered during the study transfusion support period will be of the assigned treatment arm as often as feasible without compromising patient care. Transfusions will be administered according to local institutional policy and safety standards as ordered by the medical team for patient care needs.

During the transfusion support period (i.e., for the 28-day initial acute transfusion period and, if appropriate, the 6 months extension period), all AEs, SAEs, TRs and UADEs will be collected starting from the initiation of the first study transfusion through exactly 28 days after the last study transfusion. SAEs are required to be reported by the Investigator to the Sponsor or designee immediately (i.e., no more than 24 hours after learning of the event). In an inpatient setting, daily bleeding status and safety events will be collected daily following each study transfusion until discharge or death, whichever is first. In the outpatient setting, if the subject is not seen by study staff for any other reason, surveillance calls are to be completed at least monthly (at minimum every 35 days) to collect AEs, SAEs, TRs, and UADEs starting from the initiation of the first study transfusion through the entire transfusion support period and through 28 days after the final study transfusion. If the monthly surveillance call interval coincides with a study visit, the surveillance call is not required as the study visit assessments take precedent.

Most proximate vital signs in the medical record will be collected prior to and following each study transfusion. The subject's hemoglobin value will be collected, (from the medical record if available) prior to and following each study transfusion episode (15 minutes to 24-hour post transfusion episode and before the next RBC transfusion). A hematology panel will be performed on pre-transfusion samples.

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Relevant concomitant medications administered, and blood products transfused from first study transfusion through 28 days following the last study transfusion will be recorded on the electronic data capture system (EDC) with indication, total daily dose, and dates of administration.

For pediatric patients, the volume of the intended transfusion should be recorded. The transfusing staff will record the proportion of the unit that was transfused and if for any reason a unit is not fully transfused, they will record the percentage of the bag that was transfused (i.e., 75%, 50%, 25%) and the reason why the remainder of the unit was not transfused or the why the transfusion was stopped. This proportion will be recorded for each unit of blood transfused and combined with the hemoglobin concentration and net volume of the RBC component measured at the blood center and the actual hemoglobin mass transfused calculated.

A negative antibody screen for IBS RBCs should be confirmed each time a standard of care ABO Type, Rh and Screen (IAT) test is performed within the 28-day acute transfusion period and the 6-month extension period, if applicable, and prior to transfusing the patient with IBS RBCs.

Anesthesia, surgical, and other procedures will be performed according to the local standards of the institution. Study RBC components will be ordered and administered to study patients by their treating physicians, also according to the local standards of care. Randomized patients who do not receive any RBC transfusion within 28 days of randomization will be withdrawn and will not be followed any longer. No additional data will be collected for these patients, nor will they be included in the data analysis. These subjects may be reassessed for eligibility and re-enrollment after withdrawal.

For SCD patients undergoing regular RCE, the following parameters should be assessed before and 15 mins to 4 hours after each RCE procedure:

- Hematology panel;
- Reticulocytes;
- Proportion (%) of HbS, HbA, and HbF;
- Coagulation panel;
- Plasma frozen sample for determination of S-300 and GSH concentrations.

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6.1.3 Day 14 (±7) days after each RCE procedure for SCD patients undergoing regular RCE

- Hematology panel;
- Reticulocytes;
- Proportion (%) of HbS, HbA, and HbF.

This visit and laboratory evaluation should be in addition to the planned Day 28 visit described below with at least one week separation between the visits.

6.1.4 Follow-Up and End of Study (Day 28 (± *7* days) and Day 75 (±15 days) of Follow-Up Period)

Day 1 of the follow-up period is the first day after the last study transfusion (either at the end of the 28-day acute transfusion period, or the 6-month extension period, or at the end of the 10th transfusion episode for repeated simple transfusion subject, or after the 3rd RCE in sickle cell subjects). In the outpatient setting if the subject is not seen by study staff for any other reason, surveillance calls are to be completed at least monthly (at minimum every 35 days) to collect AEs, SAEs, TRs, and UADEs starting from the initiation of the first study transfusion through the entire transfusion period and through 28 days after the final study transfusion. If the monthly surveillance call interval coincides with a study visit, the surveillance call is not required as the study visit assessments take precedent..

6.1.5 Day 28 (± *7* days) Follow-Up Assessments After Last Study Transfusion or Before First Post-Study RCE With Conventional RBCs in Patients On A Regular RCE Program

On Day 28 (± *7* days) after the last study transfusion in the study RBC support period, patients will undergo the following assessments: vital signs, AEs, SAEs, TRs, comorbid conditions, blood samples for safety labs (hematology panel, blood chemistry panel, coagulation panel), IAT and DAT, and immune reactivity to IBS RBCs. Samples may be used for additional in vitro research testing as required to confirm transfusion-transmitted pathogen mediated infections.

For SCD patients undergoing regular RCE, the following assessments should be collected:

- Hematology panel;
- Reticulocytes;
- Proportion (%) of HbS, HbA, and HbF;

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- Plasma frozen sample for determination of S-300 and GSH concentrations.

6.1.6 Day 75 of Follow-Up (75 Days ±15 days) After Last Study Transfusion - End of Study)

On Day 75 of the follow-up period (75 ± 15 days) days after the last study transfusion in the study RBC support period), a blood sample will be collected for immune reactivity test for IBS RBC and DAT.

6.2 Concomitant and Excluded Therapy

During the study standard medical care according to local institutional standards will be provided to each patient. Patients with planned use of autologous or directed donations will be excluded from the study.

Patients who have received investigational products, including investigational blood products, pharmacologic agents or imaging materials, within 28 days prior to randomization are not eligible, but may be rescreened at a later date.

Patients that are found to be eligible, including all lab assessments and S-303 antibody screen, but then are transfused with non-study RBCs prior to randomization, may be randomized and those Screening assessments listed in Table 7-1, Table 7-2 and 7-3 should be repeated prior to the first study transfusion.

6.3 Treatment Compliance

Treatment compliance will be overseen by the Investigator and study staff and relevant documentation will be recorded in the CRF. Compliance will be monitored by the Sponsor and/or Sponsor's representatives by review of source documents. The study RBC components will be labeled and tracked through all stages of processing of Test and Control components, storage, issue, and transfusion.

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7 STUDY ASSESSMENTS

7.1 Assessments

The study assessments used to evaluate safety in the study are presented in **Table 7-1** (bleeding and non-bleeding patients: 28-day); **Table 7-2** (non-bleeding patients receiving repeated transfusions: 28-day +6-month) and **Table 7-3** (SCD on regular RCE: 28-day +6-month).

Table 7-1 Schedule of 28-Day Study Assessments for Patients Requiring Simple RBC Transfusions

Patient population: Bleeding and non-bleeding patients, all indications

Study Assessments	Screening	Transfusion Support Period (Day 1 through Day 28, or death)		Follow-Up Visit Day 28* (28±7 days) after last study transfusion	End of Study-Day 75 of Follow-Up (75±15 days) after last study transfusion
		Before each transfusion episode	15min - 24 hr after each transfusion episode		
Informed Consent (assent, if appropriate)	X[1]				
Medical, surgical, prior transfusion and medication history	X[1]				
Physical exam, including height	X[1]				
Weight	X[1]				
Demographics	X[1]				
ABO Blood type and Rh[3]	X[1]	X[3]			
Indirect Antiglobulin Test[3]	X[1]	X[3]		X	
DAT[8]	X[1]			X	X
Immune reactivity to IBS RBC (S-303 antibody testing)	X[1]	X[7]		X	X
Pregnancy test (if applicable)[3]	X				
Indication for RBC transfusion	X[1]				
Hematology panel[9]	X[1]	X		X	
Hemoglobin Measurement			X[2]		
Blood chemistry panel[10]	X[1]	X		X	
Coagulation panel[11]	X[1]			X	
Vital signs	X[1]	X	X	X	
RBC transfusion data (study or non-study)	X[1]	X		X[5]	
Concomitant medications	X[1]	X[4]		X	

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Study Assessments	Screening	Transfusion Support Period (Day 1 through Day 28, or death)		Follow-Up Visit Day 28* (28±7 days) after last study transfusion	End of Study-Day 75 of Follow-Up (75±15 days) after last study transfusion
		Before each transfusion episode	15min - 24 hr after each transfusion episode		
Other blood Components transfused		X		X	
Procedure details (as applicable, e.g., surgery)		X			
Adverse events and transfusion reactions		X	X	X[13]	
SAEs		X	X	X[13]	
Surveillance Calls [12]		X		X	
Documentation of vital status		X		X	X
Assess proportion of each RBC component transfused (e.g., 25%, 50%, 75% or 100%). For pediatric patients, the volume of the intended transfusion should be recorded.			X		
Assessment of bleeding status[6]	X	X			

* Day 1 of the follow-up period is the first day after the last study transfusion.

1 If results from the Screening assessments listed are available in the medical record within 30 days prior to randomization, those data may serve as the screening data and the assessments do not need to be repeated unless the subject has an RBC transfusion in the 30-day period. If an RBC transfusion occurs after determined eligibility but prior to randomization, the subject may be randomized, and those Screening assessments listed above should be repeated prior to the first study transfusion.

2 Hb measurement at 15 minutes to 24 hours post transfusion episode (before the next RBC transfusion episode)

3 Routine standard of care test order per local hospital SOPs

4 Medications administered during anesthesia for surgical or other procedures are not collected

5 The date of non-study RBC transfusion, if any, during the 28-day follow up period and 6-month extension, if applicable, must be documented

6 Daily for inpatients when available through the end of the acute transfusion period for inpatients

7 Performed in conjunction with every routine standard of care test for ABO Type, Rh and screen (IAT) test that is performed during the Acute Support Period

8 If, during the acute support period or follow up assessments (Day 28), a positive DAT result is observed, participating sites will follow their routine standard practice for confirmation/characterization of DAT positive samples; this should only apply to any conversion from a negative to a positive DAT after enrollment, that is not part of an investigation of hemolysis or of a positive IAT with evidence of an S-303 antibody, in which case further investigations may be appropriate after discussion with the sponsor.

9 Hematology Panel: WBC, RBC, Hb, Hct, MCV, MCH, MCHC, MPV, RDW, PLT, Neut %, Mono%, Lymph%, Baso%, Eos%

10 Blood Chemistry Panel: BUN, Creat, EGFR, NA, K, GLU, Cl, CO_2, TP, ALB, ALKP, AST (SGOT), ALT (SGPT), LDH, CPK, TBIL, DBIL

11 Coagulation Panel: PT, INR, APTT, Fibrinogen

12 In the outpatient setting if the subject is not seen by study staff for any other reason, surveillance calls are to be completed at least monthly (at minimum every 35 days) to collect AEs, SAEs, TRs, and UADEs starting from the initiation of the first study transfusion through the entire transfusion support period and through 28 days after the final study transfusion. If the monthly surveillance call interval coincides with a study visit, the surveillance call is not required as the study visit assessments take precedent.

13 AEs, SAEs, TRs, and UADEs are collected from initiation of the first study transfusion through exactly 28 days after the last study transfusion.

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Table 7-2 Schedule of 28-day +6-Month Extension Period Assessments for Patients Receiving Repeated Simple Transfusions

Patient population: Non-bleeding Patients with Thalassemia, SCD, MDS, AA, Chemotherapy or other bone marrow failure syndromes.

Study Assessments	Screening	Transfusion Support Period (Day 1 through Day 28 plus 6-month extension or death-up to 10 transfusion episodes)		Follow-Up Visit Day 28* (28±7 days) after last study transfusion episode	End of Study-Day 75 of Follow-Up (75±15 days) after last study transfusion
		Before each transfusion episode	15 min - 24 hr after each transfusion episode		
Informed Consent (assent, if appropriate)	X[1]				
Medical, surgical, prior transfusion and medication history	X[1]				
Physical exam, including height	X[1]				
Weight	X[1]				
Demographics	X[1]				
ABO Blood type and Rh[3]	X[1]	X[3]			
Indirect Antiglobulin Test[3]	X[1]	X[3]		X	
DAT[8]	X[1]			X	X
Immune reactivity to IBS RBC (S-303 antibody testing)	X[1]	X[7]		X	X
Pregnancy test (if applicable)[3]	X				
Indication for RBC transfusion	X[1]				
Hematology panel[9]	X[1]	X		X	
Hemoglobin Measurement			X[2]		
Blood chemistry panel[10]	X[1]	X		X	
Coagulation panel[11]	X[1]			X	
Vital signs	X[1]	X	X	X	
RBC transfusion data (study or non-study)	X[1]	X		X[5]	
Concomitant medications	X[1]	X[4]		X	
Other blood components transfused		X		X	
Procedure details (as applicable, e.g., surgery)		X			
Adverse events and transfusion reactions		X	X	X[13]	

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Study Assessments	Screening	Transfusion Support Period (Day 1 through Day 28 plus 6-month extension or death-up to 10 transfusion episodes)		Follow-Up Visit Day 28* (28±7 days) after last study transfusion episode	End of Study-Day 75 of Follow-Up (75±15 days) after last study transfusion
		Before each transfusion episode	15 min - 24 hr after each transfusion episode		
SAEs		X	X	X[13]	
Surveillance calls [12]		X		X	
Documentation of vital status		X		X	X
Assess proportion of each RBC component transfused (e.g., 25%, 50%, 75% or 100%). For pediatric patients, the volume of the intended transfusion should be recorded.			X		
Assessment of bleeding status[6]	X	X			

* Day 1 of the follow-up period is the first day after the last study transfusion.

1 If results from the Screening assessments listed are available in the medical record within 30 days prior to randomization, those data may serve as the screening data and the assessments do not need to be repeated unless the subject has an RBC transfusion in the 30-day period. If an RBC transfusion occurs after determined eligibility but prior to randomization, the subject may be randomized, and those Screening assessments listed above should be repeated prior to the first study transfusion.

2 Hb measurement at 15 minutes to 24 hours post transfusion episode (before the next RBC transfusion episode)

3 Routine standard of care test order per local hospital SOPs

4 Medications administered during anesthesia for surgical or other procedures are not collected

5 The date of non-study RBC transfusion, if any, during the 28-day follow up period and 6-month extension, if applicable, must be documented

6 Daily for inpatients when available through the end of the acute transfusion period for inpatients

7 Performed in conjunction with every routine standard of care test for ABO Type, Rh and screen (IAT) test that is performed during the Acute Support Period and 6-Month Extension.

8 If, during the acute support period or follow up assessments (Day 28), a positive DAT result is observed, participating sites will follow their routine standard practice for confirmation/characterization of DAT positive samples; this should only apply to any conversion from a negative to a positive DAT after enrollment, that is not part of an investigation of hemolysis or of a positive IAT with evidence of an S-303 antibody, in which case further investigations may be appropriate after discussion with the sponsor.

9 Hematology Panel includes: WBC, RBC, Hb, Hct, MCV, MCH, MCHC, MPV, RDW, PLT, Neut %, Mono%, Lymph%, Baso%, Eos%

10 Blood Chemistry Panel includes: BUN, Creat, EGFR, NA, K, GLU, Cl, CO_2, TP, ALB, ALKP, AST (SGOT), ALT (SGPT), LDH, CPK, TBIL, DBIL

11 Coagulation Panel: PT, INR, APTT, Fibrinogen.

12 In the outpatient setting if the subject is not seen by study staff for any other reason, surveillance calls are to be completed at least monthly (at minimum every 35 days) to collect AEs, SAEs, TRs, and UADEs starting from the initiation of the first study transfusion through the entire transfusion support period and through 28 days after the final study transfusion. If the monthly surveillance call interval coincides with a study visit, the surveillance call is not required as the study visit assessments take precedent

13 AEs, SAEs, TRs, and UADEs are collected from initiation of the first study transfusion through exactly 28 days after the last study transfusion.

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Table 7-3 Schedule of RCE Study Assessments During 28-day and 6-month Extension Period

Patient population: Sickle Cell Disease patients on a regular, repeated RCE program receiving 3 consecutive RCE procedures.

Study Assessments	Screening	Transfusion Support Period (Day 1 through Day 28 plus 6-month extension or death – 3 RCE episodes)		Follow-Up Visit Day 14 (14±7 days) after each RCE episode	Follow-Up Visit Day 28* (28±7 days) after last study RCE or prior to next non-study RCE if less than 28 days since last study RCE	End of Study-Day 75 of Follow-Up (75±15 days) after last study transfusion
		Before each RCE episode	15min – 4 hr after each RCE episode			
Informed Consent (assent, if appropriate)	X[1]					
Medical, surgical, prior transfusion[2] and medication history, (incl. basis of SCD diagnosis and G6PD status)	X[1]					
Physical exam, including height	X[1]					
Weight	X[1]					
Demographics	X[1]					
ABO Blood type and Rh[3]. Extended Phenotype, if available	X[1]	X[3]				
Indirect Antiglobulin Test[3]	X[1]	X[3]			X	
DAT[8]	X[1]				X	X
Immune reactivity to IBS RBC (S-303 antibody testing)	X[1]	X[7]			X	X
Pregnancy test (if applicable)[3]	X					
Indication for RBC transfusion	X[1]					
Hematology panel and reticulocytes[9]	X[1]	X	X	X	X	
% HbS, HbA, HbF	X[1]	X[2]	X[2]	X	X	
Blood chemistry panel[10]	X[1]	X			X	
Coagulation panel[11]	X[1]	X	X		X	
S-300 and GSH (frozen plasma)		X	X		X	
Vital signs	X[1]	X	X		X	

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Study Assessments	Screening	Transfusion Support Period (Day 1 through Day 28 plus 6-month extension or death – 3 RCE episodes)		Follow-Up Visit Day 14 (14±7 days) after each RCE episode	Follow-Up Visit Day 28* (28±7 days) after last study RCE or prior to next non-study RCE if less than 28 days since last study RCE	End of Study-Day 75 of Follow-Up (75±15 days) after last study transfusion
		Before each RCE episode	15min – 4 hr after each RCE episode			
RBC transfusion data (study or non-study)	X[1]	X			X[5]	
Concomitant medications	X[1]	X[4]			X	
Other blood components transfused		X			X	
RCE Procedure details			X			
Adverse events, AESI and transfusion reactions		X	X	X	X[13]	
SAEs		X	X	X	X[13]	
Surveillance Calls [12]		X		X	X	
Documentation of vital status		X			X	X
Assess proportion of each RBC component transfused (e.g., 25%, 50%, 75% or 100%). For pediatric patients, the volume of the intended transfusion should be recorded.			X			
Assessment of bleeding status[6]	X	X				

*Day 1 of the follow-up period is the first day after the last study transfusion.

1 If results from the Screening assessments listed are available in the medical record within 30 days prior to randomization, those data may serve as the screening data and the assessments do not need to be repeated unless the subject has an RBC transfusion in the 30-day period. If an RBC transfusion occurs after determined eligibility but prior to randomization, the subject may be randomized, and those Screening assessments listed above should be repeated prior to the first study transfusion.

2 Including pre- and post-transfusion Hb and % HbS, HbA, and HbF levels for prior 6 months if available and RBC volume transfused monthly for prior 6 months.

3 Routine standard of care test order per local hospital SOPs

4 Medications administered during anesthesia for surgical or other procedures are not collected

5 The date of non-study RBC transfusion, if any, during the 28-day follow up period and 6-month extension, if applicable, must be documented

6 Daily for inpatients when available through the end of the acute transfusion period for inpatients

7 Performed in conjunction with every routine standard of care test for ABO Type, Rh and screen (IAT) test that is performed during the Acute Support Period and 6-Month Extension.

8 If, during the acute support period or follow up assessments (Day 28), a positive DAT result is observed, participating sites will follow their routine standard practice for confirmation/characterization of DAT positive samples; this should only apply to any conversion from a negative to a positive DAT after enrollment, that is not part of an investigation of hemolysis or of a positive IAT with evidence of an S-303 antibody, in which case further investigations may be appropriate after discussion with the sponsor.

9 Hematology Panel: WBC, RBC, Hb, Hct, MCV, MCH, MCHC, MPV, RDW, PLT, Neut %, Mono%, Lymph%, Baso%, Eos%, reticulocytes

10 Blood Chemistry Panel: BUN, Creat, EGFR, NA, K, GLU, Cl, CO_2, TP, ALB, ALKP, AST (SGOT), ALT (SGPT), LDH, CPK, TBIL, DBIL

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[11] Coagulation Panel: PT, INR, APTT, Fibrinogen.

[12] In the outpatient setting if the subject is not seen by study staff for any other reason, surveillance calls are to be completed at least monthly (at minimum every 35 days) to collect AEs, SAEs, TRs, and UADEs starting from the initiation of the first study transfusion through the entire transfusion support period and through 28 days after the final study transfusion. If the monthly surveillance call interval coincides with a study visit, the surveillance call is not required as the study visit assessments take precedence.

[13] AEs, SAEs, TRs, AESIs and UADEs are collected from initiation of the first study transfusion through exactly 28 days after the last study transfusion.

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7.2 Assessment of Efficacy

The Efficacy Endpoints are:

- Primary (all non-bleeding patients at baseline, excluding RCE patients): Adjusted hemoglobin increment, defined as the difference between the pre-transfusion and post transfusion (taken within 15 minutes to 24 hours of a transfusion episode) hemoglobin values divided by the total hemoglobin content transfused, averaged over one or more transfusion episodes in patients without active bleeding at baseline (active bleeding is defined as WHO Grade 3 or 4 bleeding).
- Secondary (all non-bleeding, chronically transfused patients in 28 day +6-month extension study, excluding RCE patients): Adjusted hemoglobin consumption, defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (g/kg/day), in patients without active bleeding at baseline.

Data from the initial 28-day period and the extension period will be integrated in the final analysis and will also be assessed separately.

For SCD patients enrolled into the 28-day +6-month extension for three RCE procedures, the efficacy assessment is a comparison of the mean of the difference in the HbA clearance rate (g/dL/day) between the Test subjects (INTERCEPT RBC) versus the Control subjects (conventional RBCs) in patients who receive 3 consecutive study RCE procedures.

7.2.1 Methods and Timing of Efficacy Parameters

The efficacy endpoints are the hemoglobin increment post transfusion adjusted by hemoglobin content transfused and the mean consumption of hemoglobin normalized for patient body weight and time. For each efficacy evaluation period, hemoglobin increment post transfusion, will be calculated on a per transfusion episode basis as the difference between the hemoglobin value most proximate before each transfusion episode and 15 minutes to 24 hours post transfusion episode, adjusted by hemoglobin content transfused. The analysis for the primary and secondary efficacy endpoints will assess the treatment difference in means between Test and Control groups via a non-inferiority test.

Adjusted consumption of hemoglobin is defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (g/kg/day). The efficacy analysis will assess the treatment

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difference in means between Test and Control RBC via a non-inferiority hypothesis test.

If a patient receives any transfusion of off-protocol RBC components, the date, volume and hemoglobin mass will be recorded. The date of the first non-study RBC transfusion, if any, during the follow up period must be documented to allow calculation of the last study transfusion episode period.

7.2.1.1 Measurement of Hemoglobin Transfused

The hemoglobin mass of each transfusion episode is the sum of the hemoglobin content for all RBC components transfused. An RBC transfusion episode is defined as consecutive RBC units transfused until the next post transfusion Hb determination with ≤12 hours between each transfusion (from the end of a prior component transfused to the start of a subsequent component transfused). The hemoglobin content of each component transfused is calculated using the hemoglobin concentration and net volume of the RBC component (measured at the blood center), and the proportion of the unit transfused (assessed at the hospital i.e., 100%, 75%, 50%, 25%). For incomplete transfusions, the transfusing staff will be responsible to assess and record the proportion of the unit that was transfused. This proportion will be recorded for each unit of blood transfused and used to calculate the actual volume transfused and corresponding hemoglobin mass content transfused. For pediatric patients, the volume of the intended transfusion should be recorded.

7.3 Assessment of Safety

7.3.1 Safety Parameters

7.3.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product (ICH E2A II/A/1, 21CFR 312.32).

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7.3.1.2 Definition of Adverse Events of Special Interest for SCD Patients Undergoing regular repeated RCE

AESIs include specific neurologic and hematologic complications associated with patients on chronic transfusion therapy for sickle cell disease. For the purposes of this study, AESI include the verbatim terms; associated preferred terms (PT) and lower-level terms (LLT) shown in **Table 7-4.**

Table 7-4 Adverse Events of Special Interest

Verbatim Term	MedDRA PT (version 19.0)	MedDRA LLT (version 19.0)
Acute pain crises (vaso-occlusive disease)	Sickle cell anaemia with crisis	Vaso-occlusive crisis
Acute chest syndrome	Acute chest syndrome	*(same)*
Stroke	Cerebrovascular accident	Stroke
Acute renal failure	Acute kidney injury	Acute renal failure
Priapism	Priapism	*(same)*
Splenic sequestration	Hypersplenism	Splenic sequestration
Avascular necrosis	Osteonecrosis	Avascular necrosis
Leg ulcers	Skin ulcer	Leg ulcer
Pulmonary hypertension	Pulmonary hypertension	*(same)*
Severe bacterial infection	Bacterial infection	Infection bacterial
Multisystem organ failure	Multiple organ dysfunction syndrome	*(same)*
Proliferative sickle cell retinopathy	Retinopathy sickle cell	Proliferative retinopathy
Deep vein thrombosis	Deep vein thrombosis	*(same)*
Pulmonary embolism	Pulmonary embolism	*(same)*

7.3.1.3 Definition of Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death
- Life-threatening event (results in an immediate risk of death from the reaction as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

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- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and/or may require intervention to prevent one of the outcomes listed in this definition.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, life-threatening or death according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria). Severity and seriousness need to be assessed for each adverse event recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours) after learning of the event (see **Section 7.4** for reporting instructions).

7.3.1.4 Unexpected/Unlisted Adverse Event

Any AE occurring in one or more patients in a research protocol, the nature, severity, or frequency of which is not consistent with (a) the applicable product information (protocol, informed consent, Investigator's Brochure or other product labeling), or (b) the expected natural progression of any underlying disease, disorder or condition of the patient experiencing the adverse event and the patient's predisposing risk factor profile for the adverse event.

7.3.1.5 Unanticipated Adverse Device Effects (UADE)

Any SAE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

7.3.1.6 Definition of Transfusion Reactions (TR)

A TR is defined as an undesirable response or effect in a patient temporally associated with and causally related to the administration of blood or blood components. The CDC NHSN Protocol definitions must be used when recording TR terms in this study (**APPENDIX 1, 2 & 3**).

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7.3.1.7 Clinically Significant Antibodies

Clinically significant antibodies (Chapman et al. 2004; Garratty 2012) are those capable of causing patient morbidity due to accelerated destruction of a significant proportion of transfused red cells.

7.3.1.8 Delayed Serological Transfusion Reaction (DSTR)

The DSTRs (Ness et al. 1990; Garratty 2012) are where a particular alloantibody can be shown to be present in the patient's plasma, on the transfused donor RBCs and/or in an eluate from these RBCs, but no clinical or laboratory signs of hemolytic anemia (HA) are present. Regardless of the mechanism, the persistence of a positive DAT does not correlate with the presence or absence of clinical hemolysis (Ness et al. 1990).

The DSTR may be in the form of new antibodies or a rising titer of antibody in patients with pre-existing antibodies (patients with pre-existing S-303 antibodies at baseline evaluation will be excluded in RedeS).

7.3.1.9 Delayed Hemolytic Transfusion Reaction (DHTR)

A DHTR (Ness et al. 1990) is defined as a DSTR that showed clinical and/or laboratory evidence of hemolysis. In the event of a confirmed DHTR, differential diagnoses of hemolytic transfusion reactions listed in **Table 7-5**: should be considered.

7.3.1.10 Acute Hemolytic Transfusion Reaction (AHTR) (Ness et al. 1990)

An AHTR is defined as the rapid destruction of RBCs during, immediately after, or within 24 hours of cessation of transfusion. Clinical and laboratory signs of hemolysis are present (CDC NHSN Hemovigilance Module Surveillance Protocol 2014).

7.3.1.11 Hyper-hemolysis Syndrome

Hyperhemolysis is characterized by a hemolytic transfusion reaction that leads to a life-threatening anemia, with drops in Hemoglobin (Hb) and Hematocrit (Hct) to levels markedly lower than those present before transfusion.

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Table 7-5: Some Differential Diagnoses of Hemolytic Transfusion Reactions

Immunologically caused hemolysis
Autoimmune hemolytic anemia
'Warm' antibody induced hemolytic anemia
Cold hemagglutinin disease
Paroxysmal cold hemoglobinuria
Drug induced immune hemolytic anemia
Passenger lymphocyte syndrome after stem cell or solid organ transplantation
Hemolytic disease of a newborn
Acute episodes of non-immunologically caused hemolysis
Hereditary erythrocyte defects
Defects of red blood cell (RBC) enzymes (e.g. glucose-6-phosphate dehydrogenase deficiency)
Hemoglobinopathies (e.g. sickle cell disease)
Thalassemia
Defects of RBC membrane
Congenital erythropoietic porphyria
Paroxysmal nocturnal hemoglobinuria
Infections
Bacterial (bartonellosis; hemolytic-uremic syndrome caused by enterohemorrhagic *Escherichia coli*; severe infections by bacteria producing hemolyzing toxins (e.g. *Clostridium perfringens*))
Protozoal (malaria, babesiosis)
Mechanical hemolysis by artificial heart valves or by extracorporeal circulation
Thrombotic-thrombocytopenic purpura (Moschowitz disease)
HELLP syndrome during gravidity
Intoxications
Near drowning

Source: Strobel E. 2008.

7.3.2 Methods and Timing of Safety Parameters

7.3.2.1

The primary safety measures are the proportion of all transfused patients with TEAEs possibly, probably or definitely related to study RBC transfusion 28 days after the last study transfusion and the proportion of patients with treatment-emergent antibodies with confirmed specificity to IBS RBCs. Only patients who receive at least one study RBC component will be included in the safety reporting and analysis.

Additional safety assessments will include, but not be limited to:

- Treatment-emergent adverse events through 28 days following the last study transfusion

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- Transfusion reactions defined by the CDC NHSN Hemovigilance Module Surveillance Protocol through 28 days following the last study transfusion
- Frequency of treatment-emergent immunization to RBC allo-antigens
- Mortality from any cause during study
- Number and volume of study RBC units transfused through 28 days after the first study transfusion
- Number of platelet and plasma components transfused

7.3.3 Assessment of Immune Reactivity to IBS RBCs

At the time of RBC crossmatch and at specified times during the study (screening, at each time an Antibody Screen (IAT) test is performed as routine standard of care during the acute support period, the extension transfusion period, at 28 days (± 7) post last study transfusion, and at the end of study (day 75± 15 days post last study transfusion)). The RBC screening panel uses a gel card agglutination format and has been validated for this purpose. The primary reagent red cell screening panel is composed of RBCs from 3 blood group O donors with defined phenotypes and is analogous to routine antibody screening panels used in regular blood banking practice. The secondary RBC screening panel is composed of reagent RBCs from an additional 6 blood group O donors with defined phenotypes and is analogous to antibody identification/characterization panels used in routine practice in blood banks to identify antibody specificity for a range of clinically relevant RBC alloantigens and is used if reactivity is detected in the primary screening assay. The panel donors were specifically antigen-phenotyped for major blood group systems similar to the commercially available reagent cells panels for antibody identification and differentiation. The primary screening and secondary RBC antibody identification panel cells have been prepared as both INTERCEPT treated and untreated RBCs. Each of the panel cell sets comprises three different RBC types: untreated RBC; treated RBCs consisting of cells carrying a “high” level of S-303 adducts (comparable to the S-303 RBCs prepared with the original process); and RBC carrying a “low” level of S-303 adducts (representative of S-303 RBCs prepared with the current generation process). The primary screening panel is designed as a sensitive screening test for both common RBC alloantibodies and for S-303 antibodies. The secondary panel is designed to determine the specificity of any antibodies detected in the primary screen and to distinguish common RBC alloantibodies from S-303 specific antibodies.

By including cells with high S-303 adducts there is increased sensitivity for antibody

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against acridine adducts and, much in the same way that homozygous donors are used to produce commercially prepared red cells, there is a greater potential for detecting low affinity or low titer (weak) antibodies. Thus, the panels have the capability to detect an antibody specific to IBS RBC even in the presence of alloreactivity from an intrinsic antigen. Including cells with low S-303 adducts provides an antigenic profile that is representative of the current clinical process and can aid antibody specificity determination.

The patient samples are tested against the panel(s) of reagent RBCs to identify an antibody specific to INTERCEPT treated RBCs. The gel card agglutination test results are scored (0, weak positive, 1+, 2+, 3+, 4+) and the reactivity is classified as follows (see **APPENDIX 4**):

- If the antibody screening score is 0 for all the untreated and INTERCEPT treated RBCs on the primary RBC screening panel, the sample is considered "non-reactive for S-303 antibodies" with no antibodies (either an intrinsic alloantibody or IBS RBC-specific antibody) present in the patient's serum and thus no requirement for antibody identification with the secondary antibody identification panel. Neither the secondary RBC screening panel nor additional tests are required. The patient continues to receive study RBC components according to the protocol.

- If the results of the primary RBC screening panel show concordant 1/3, 2/3, or 3/3 reactive with BOTH the INTERCEPT treated reagent RBCs and the corresponding Control untreated RBCs, the sample will be considered "presumed allo-reactive" to an intrinsic red cell antigen. The sample is tested against the secondary RBC screening panel to identify and confirm the specificity of the allo-antibody producing the reaction according to standard blood banking rules (reactivity with three RBC cells bearing the RBC antigen, and non-reactivity with three RBC that lack the antigen). If the antibody that is causing the agglutination is identified and confirmed, then the sample is considered "allo-reactive" for that RBC alloantigen. In this setting, lack of reactivity with all (at least three) INTERCEPT treated RBC cells that lack the RBC alloantigen, will rule out S-303 antibody specificity. The patient continues on study and will receive compatible (cross matched) study RBC components.

- If reactivity is present and S-303 antibodies cannot formally be ruled out, or agglutination is visible for all the untreated RBC cells in the panel, (i.e., "pan-reactive"), the patient will be withdrawn from the study treatment and followed for safety assessment.

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- If the primary RBC screening panel score is positive with 2/3 or 3/3 of the INTERCEPT treated RBCs carrying S-303 adducts at either 'high" and/or "low" level AND 0/3 with the corresponding Control untreated RBCs which lack S-303 adducts, the sample is classified as "reactive for S-303 antibodies" and the sample is sent to the central testing lab for further characterization (see **APPENDIX 6**: Evaluation of Reactivity with IBS RBC). The patient will be withdrawn from the study treatment, followed for safety assessment, and investigated for evidence of hemolysis.

Weak false positive test results are known to occur with serological tests due to variation in performance of the test and manual interpretation of the results (Aubuchon et al. 2008). The provisions below are put in place to ensure that patients are not inappropriately withdrawn from the study treatment and are in keeping with the current blood bank policies that repeat reactive results in a minimum of two tests are required for a positive test in serological viral marker assays.

- Should only 1/3 S-303 RBC in the primary panel test reactive for the S-303 labeled cells without reactivity for the untreated RBC, that S-303-RBC cell (at both high and low levels of S-303 adduct) and its untreated Control will be considered "initially reactive" and the test will be repeated in duplicate on that cell only (of the three cells in the primary panel), and the secondary panel will also be tested. In this setting, the secondary panel serves to increase the sensitivity for S-303 specific antibodies by testing a larger number of S-303 RBC cells. Negative reactivity to both repeat tests of the primary panel cell and negativity with the secondary panel will be considered a negative test. Reactivity in at least one of two repeat primary panel cells S-303 RBC cells or any S-303 RBC cell in the secondary panel without reactivity with the corresponding untreated RBC will be a considered positive test for S-303 reactivity. The sample will be sent for additional characterization at the central immunohematology reference center (Versiti Blood Center of Wisconsin formerly Blood Center of Wisconsin) (see **APPENDIX 6**: Evaluation of Reactivity with IBS RBC) to include inhibition studies to determine specificity of observed reactivity. The patient will be withdrawn from the study treatment and investigated for evidence of hemolysis.

The above protocol will ensure that the minimum criteria for withdrawal of a patient requires reactivity with at least two S-303-RBC cells in the panel with no reactivity with the corresponding untreated Control or repeat reactivity with a single S-303 RBC with an unreactive determination with its untreated Control.

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7.3.3.1 Investigation for Evidence of Clinical Hemolysis in the Presence of Immune Reactivity to IBS RBCs

If a subject is determined to have developed a treatment-emergent antibody to S-303 RBC, the following steps should be taken (see **Section 14.6 APPENDIX 6**: Evaluation of Reactivity with IBS RBC).

- The subject should be withdrawn from the active treatment phase of the study but should continue with all planned safety assessments per protocol.
- If the subject requires further transfusion, conventional RBC should be transfused.
- The subject should be actively investigated for signs or symptoms of intravascular or extravascular hemolysis for at least 4 weeks after the last study transfusion.
- Blood samples should be sent to the central immunohematology reference center (Versiti Blood Center of Wisconsin formerly Blood Center of Wisconsin) for assessment of the hemolytic potential and changing characteristics and titer of S-303 antibodies every 1-2 weeks for 4 weeks or until resolution of the event (see **Section 14.6 APPENDIX 6**: Evaluation of Reactivity with IBS RBC).

To discriminate whether an antibody with specificity for S-303 RBC is physiologically active or clinically significant, any one of the following criteria indicative of accelerated RBC clearance in the absence of active bleeding, organ-mediated RBC sequestration, severe erythroid hypoplasia or other concurrent medical cause for acute anemia not associated with transfusion, should be present:

a. During the first 7 days following transfusion, the patient's hemoglobin level has returned to the pre-transfusion level.

b. During Days 8-14 following transfusion, the patient's hemoglobin level has declined below the pre-transfusion hemoglobin level for this transfusion.

Beyond Day 14 post-transfusion, the assessment of a clinically significant change in the patient's post-transfusion hemoglobin level compared to prior responses for comparable hemoglobin doses transfused as judged by the Investigator.

Other clinical signs and symptoms that may be considered by the Investigator to judge whether accelerated RBC clearance is occurring, include:

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- Extravascular hemolysis
  - falling Hct
  - increased unconjugated bilirubin (≥1.5-fold higher than the upper limit of normal)
  - fever
  - positive DAT
  - micro-spherocytes on peripheral smear
- Intravascular hemolysis
  - shock syndrome
  - hypotension (BP lower than 90/60 mmHg.)
  - back pain
  - plasma free Hb increased
  - increase in lactic dehydrogenase (LDH) ≥1.5-fold higher than the upper limit of normal (LDH ≥1.5×ULN)
  - urine hemoglobin (hemoglobinuria)
  - urine hemosiderin (hemosiderinuria)
  - decreased or absent haptoglobin levels

For the purposes of this protocol, the development of a new antibody specific to S-303 treated RBCs in the patient and with evidence of accelerated IBS RBC clearance, in the absence of clinical alternative explanations (e.g., concomitant RBC alloantibodies, sickle cell disease, etc.) will be classified as an acute hemolytic transfusion reaction. All S-303 specific antibodies and all hemolytic transfusion reactions will be reported to the FDA and DSMB within 30 days. As part of the investigation of a treatment-emergent S-303 antibody, the patients' randomization assignment may be unblinded after discussion of the case(s) with the DSMB and obtaining their permission, to determine the antibody's relationship to the study transfusion and to the patient's signs and symptoms.

7.3.4 Abnormal Test Findings

Subject test results will be reviewed by the Investigator and any abnormal findings will be evaluated for clinical significance. The criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or

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- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy.
- Clinically significant laboratory findings will be recorded as adverse events. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

7.3.5 Reporting Period

Repeated Simple Transfusion Arm

The transfusion periods will comprise of 28 days from the day of the first study transfusion through Day 28 and for an additional 6-months if the subject is entered into the extension period option for up to 10 transfusion episodes or death.

RCE Arm

For SCD patients on a regular, repeated RCE program enrolled into the 28-day +6-month extension period, the study transfusion period will end after the third consecutive RCE procedure.

Day 1 of the acute transfusion period is the day of the first study RBC transfusion. Safety events consisting of AEs, SAEs, TRs, and UADEs will be collected from initiation of the first study transfusion through exactly 28 days after the last study transfusion/. Only patients who receive at least one study RBC component will be included in the safety reporting and analysis.

Samples may be used for additional in vitro research tests as required to confirm transfusion-transmitted pathogen mediated infections.

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7.4 Recording and Reporting Adverse Events

AEs, SAEs, TRs, and UADEs that occur during the transfusion periods (28 days, or 28 days plus 6-months up to 10 transfusion for repeated simple transfusion subject, or 28 days plus 6-months of 3 consecutive RCE for sickle cell subjects) will be collected and reported in the eCRF. In an inpatient setting, daily bleeding status and safety events will be collected daily following each study transfusion until discharge or death, whichever is first. In the outpatient setting if the subject is not seen by study staff for any other reason, surveillance calls are to be completed at least monthly (at minimum every 35 days) to collect AEs, SAEs, TRs, and UADEs starting from the initiation of the first study transfusion through the entire transfusion support period and through 28 days after the final study transfusion. If the monthly surveillance call interval coincides with a study visit, the surveillance call is not required as the study visit assessments take precedent. TRs will be defined and classified according to the CDC NHSN protocol, and they may be associated with different blood components (i.e., plasma, platelets and RBC). Only patients who receive at least one study RBC component will be included in the safety reporting and analysis. All TRs (regardless of the implicated blood component) will be reported in the eCRF and, if in routine use, in the NHSN Hemovigilance module up to 28 days post the last study transfusion.

The Investigator will assess the severity of each AE based on the NCI Common Terminology Criteria for Adverse Events (CTCAE).

Table 7-6 Severity Assessment of Adverse Events

Grade 1: Mild asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Link to NCI CTCAE 4.03: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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7.4.1.1 Assessing Seriousness of an Adverse Event

The Investigator will assess if an AE resulted in any of the following outcomes that result in classification of the event as an SAE: death, a life-threatening event (results in an immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or another important medical event (**Section 7.3.1**).

7.4.1.2 Assessing Causality of an Adverse Event

The Investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. If the Investigator does not know whether investigational product caused the event, then the event will be handled as "possibly related to investigational product" for reporting purposes. If the Investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on trial records and considered unrelated for reporting purposes.

AEs assessed by the Investigator to be related (possible, likely/probable, certain/definite) to the investigational product must be evaluated as a TR and classified per the CDC NHSN HV Protocol (**APPENDIX 1, 2 & 3**).

In addition, if the Investigator determines a serious adverse event is associated with trial procedures, the Investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

The standard nomenclature for defining the causal relationship between an AE and the study product is listed in the following table.

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Table 7-7 Relationship between Investigational Product and Adverse Events

Imputability Level	Explanation
Excluded	When there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to alternative causes
Unlikely	When the evidence is clearly in favor of attributing the adverse event to causes other than the study transfusion
Possible	When the evidence is indeterminate for attributing the adverse event to the study transfusion or an alternate cause
Likely/Probable	When the evidence is clearly in favor of attributing the adverse event to the study transfusion
Certain/Definite	When there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to the study transfusion

7.4.1.3 Assessing Relationship to the INTERCEPT Blood System Device

The Clinical Investigator in collaboration with the blood transfusion service staff will assess whether there is a reasonable possibility that the IBS medical device used for preparation and or processing of the blood component caused or contributed to an AE. Determination of whether there is a reasonable possibility that an INTERCEPT component caused or contributed to an AE includes assessing whether a device malfunction occurred during the preparation of the blood component.

7.4.1.4 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow regional and international regulations, as appropriate.

If an SAE occurs, the Investigator must notify Cerus or its designated representative within 24 hours after becoming aware of the event. When reporting SAEs to Cerus, the Investigator will ensure the report includes the safety assessments detailed in **Section 7.3**.

Recording the data directly into the eCRF is the preferred method to transmit this information to the project contact for SAE receipt. In circumstances where the Investigator is unable to record the data on the eCRF, the Investigator notifies Cerus Global Product Safety directly (within 24 hours of learning of the event). Sponsor contact information is provided in **Table 7-8.**

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Table 7-8 Cerus Global Product Safety Contact Information

Name Title	Phone	E-mail
Richard Benjamin, MD, PhD Chief Medical Officer	Office: (925) 288-6020 Mobile: (703) 945-9277	RBenjamin@cerus.com
Marissa Li, MD Senior Director of Clinical Development & Medical Affairs Global Product Safety (Medical Monitor)	Mobile: (310) 980-2780	MLi@cerus.com
Cerus Global Product Safety	Please contact via E-mail	RedeSSafety@cerus.com

Investigators must also comply with local requirements for reporting SAE to the Institutional Review Board/Ethics Committee (IRB/EC).

For all SAEs, the Investigator is obligated to pursue and provide information to Cerus or its representative in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Cerus or its designee to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings and/or death certificate should be submitted as soon as possible to Cerus or its designated representative.

7.4.2 Reporting Device Malfunctions

Blood centers are required to report any malfunctions of the IBS medical device on the eCRFs. If a device malfunction impacts the health of a person (patient, user or other) during the study, it is also considered an AE. The Investigator must notify Cerus Product Safety per **Section 7.4.1.4**. Sponsor contact information is provided in **Table 7-8**. If a component malfunction occurs at the participating hospitals sites, the site will complete a Component Complaint Form.

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7.5 Data Safety Monitoring Board (DSMB)

The study data will be monitored on a regular basis by a DSMB. The primary responsibility of the DSMB is to ensure patient safety. The DSMB will be assembled by the Sponsor and composed of transfusion medicine experts and a non-voting statistician. DSMB members will be independent of the Sponsor. The DSMB will review safety data after approximately half of the patients have been enrolled and treated (n~300), at any time that safety or enrollment rate concerns arise and as defined in the DSMB charter. The DSMB will review unblinded safety and efficacy data at the conclusion of the study or at premature termination. An unblinded statistician will provide the DSMB with blinding codes in a sealed envelope if the DSMB will require this information to make its recommendations. The DSMB and/or the FDA could recommend an early conclusion of the trial based on the stopping rules detailed in **Section 7.6**.

Cerus will notify the DSMB of a fatal outcome assessed to be possibly, probably, or definitely related to the study product and confirmed S-303 antibody associated transfusion reactions within 72 hours of becoming aware of the event. Cerus will submit a full written report to the DSMB within 7 days. The DSMB will provide comments back to Cerus within 48 hours of receipt of the full report.

7.6 Enrollment Pause and Stopping Rules

7.6.1 Definitions

7.6.1.1 Enrollment Pause

“Enrollment Pause” means new patients will not be enrolled in the study while investigations are ongoing. An enrollment pause may be requested by Cerus, the DSMB or the FDA to allow time to investigate potential safety signals. Patients already on study and receiving study RBC transfusions will continue to receive study transfusions and complete all study procedures. The study may continue enrollment of new patients following consultation with the DSMB. The DSMB and FDA will be notified of enrollment pauses and decisions to continue enrollment.

Clinical Stop

“Clinical Stop” means complete cessation of recruitment activities and all study transfusions, thus stopping the active study transfusion phase of the study. Patients will continue receiving non-study conventional transfusions as needed. All safety monitoring tasks will continue as per protocol.

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7.6.2 Rules

Study may be temporarily paused or definitively stopped based on the following rules/considerations:

a) Poor/slow accrual: The goal is to recruit up to 800 transfused patients in the study. The Sponsor can stop the study if fewer than 300 patients are enrolled over a period of 12 months, which would suggest that there is less than anticipated need for access to this treatment mode.

b) Safety

- Patients who are required or expected to require a transfusion of RBC component(s) are eligible to participate in this study. There are no accurate estimates in the literature on the frequency of SAEs or TRs in randomized clinical trials with transfused RBCs and an active safety/ hemovigilance data collection paradigm. Thus, it is not possible to provide expected/acceptable rates of SAEs or TRs to make an informed decision to stop the study. Furthermore, given the heterogeneity of the patient population, group imbalances could heavily influence the rates of observed SAEs and TRs. Following the transfusion of half of the patients (approximately 300 patients), group-blinded data will be provided to the DSMB. DSMB will be provided with blinding codes in a sealed envelope. If the rates of SAEs or TRs are in the opinion of the DSMB, statistically or clinically higher in one treatment group, and cannot be explained by comorbid conditions or baseline imbalances between the groups, the DSMB may make recommendations for pausing, stopping, or modifying the study.

- The occurrence of S-303 specific DSTRs, DHTRs, AHTRs or hyperhemolysis syndrome in subjects exposed to IBS RBC may result in individual patient withdrawal, enrollment pause, or a clinical stop as presented in **Table 7-9**. In certain cases, enrollment or transfusion of study patients may be resumed after a stop with the authorization of the DSMB and/or FDA.

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Table 7-9 Stopping Rules

Trigger	Sponsor Action	Notify			Enrollment	On Study Patients	Continuation	Additional actions
For S-303 Specific Abs		**IRB**	**FDA**	**DSMB**				--
S-303 Specific DSTR with no evidence of hemolysis	Patient Withdrawal	X	X	X	Continue	Continue	----	Sponsor will notify DSMB and FDA of each S-303 Ab[2] Investigation may include unblinding the treatment assignment
S-303 Specific DSTR	Enrollment Continue	X	X	X	Continue	Continue [1,3]	-----	Investigate hemolytic potential. Investigation may include unblinding the treatment assignment
S-303 Specific DHTR (1 x)	Clinical Stop	X	X	X	Stop	Stop	After Investigation & discussion with FDA & DSMB	Investigate full hemolytic potential. Continuation contingent on outcome of investigation and on FDA agreement on resumption. Investigation may include unblinding the treatment assignment
S-303 Specific AHTR (1 x)	Clinical Stop	X	X	X	Stop	Stop	After Investigation & discussion with FDA & DSMB	Stop study for an S-303- specific single acute hemolytic reaction. Continuation contingent on outcome of investigation and on FDA agreement on resumption. Investigation may include unblinding the treatment assignment
S-303 -Specific Hyper-hemolysis Syndrome (x1)	Clinical Stop	X	X	X	Stop	Stop	With FDA release	Investigation may include unblinding the treatment assignment

[1] During investigation for patients continuing treatment, a full IAT crossmatch may be performed before each transfusion and a new S-303 antibody screen every third day to protect the recipients.

[2] Applies to all S-303 specific antibody examples shown in rows 1-5.

[3] See **Section 7.6.3**- Investigation of Hemolytic Potential

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7.6.3 Investigation of Hemolytic Potential

Investigation of the hemolytic potential of any S-303 RBC specific antibodies found in the RedeS study will be conducted according to the protocol in **Section 14.6 APPENDIX 6** (Evaluation of reactivity with IBS RBC). Possible studies may include:

- Antibody specificity via agglutination inhibition studies (inhibited by soluble acridine or not)
- Antibody characterization:
  - Immunoglobulin isotype and IgG subclass (IgM, $IgG_{1, 2, 3 \text{ or } 4}$)
  - Antibody titer
  - Persistence and titer over time
  - Thermal spectrum and phase of reaction
  - Complement-mediated in vitro hemolysis
- Investigation of concurrent antibodies to intrinsic RBC allo-antigens.
- Monocyte Monolayer Assay for clinical significance (Arndt and Garratty 2004)
  - Investigation may include unblinding the treatment assignment to differentiate natural and IBS RBC treatment-emergent antibodies.
  - When available, patient samples will be assessed for circulating IBS RBC using a flow cytometry assay and detection using a monoclonal antibody directed to S-300 (acridine).

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8 STATISTICS

8.1 Statistical Methods

8.1.1 Efficacy Analysis

Only patients in the modified intent-to-treat (MITT) analysis set, defined as randomized patients who receive at least one study RBC component, will be included in the efficacy analysis. MITT patients will be summarized under the treatment arm as randomized for data analysis.

The primary efficacy endpoint is defined as the difference between the pre-transfusion episode and the post-transfusion episode hemoglobin values (taken within 15 minutes to 24 hours of the end of a transfusion episode, before the next transfusion) divided by the total hemoglobin content transfused, averaged over one or more transfusion episodes, in patients without active bleeding at baseline (hereafter referred to as non-bleeding patients, and active bleeding defined as WHO Grade 3 or 4 bleeding).

The secondary efficacy endpoint is the adjusted hemoglobin consumption (g/kg/day), defined as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (that is, 28 days for the initial acute transfusion period plus 6 months for the extension period option if applicable, unless patients prematurely discontinue from the study), in non-bleeding patients. For patients who prematurely discontinue from the study, their duration of the study transfusion period will be calculated per the rules given in **Section 8.1.1** below.

Non-study RBCs received during the study transfusion period will be included to calculate the total hemoglobin content transfused for the two efficacy endpoints in the modified Intention to Treat (mITT) analysis set. Patients receiving non-study RBC transfusions during the study transfusion period will be excluded from the Per Protocol (PP) analysis set. Data from the initial 28-day period and the optional extension period will be summarized separately as well as combined in the final report.

For SCD patients enrolled into the 6-month extension for three RCE procedures, the efficacy assessment is the mean HbA clearance rate (g/dL/day) between the Test subjects (INTERCEPT RBC) versus the Control subjects (conventional RBCs).

HbA clearance rate (g/dL/day) in patients with SCD undergoing regular repeated RCE will be estimated from the area under the curve (AUC) calculated by the

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trapezoidal rule based on measurements from post-transfusion samples, 14 ±7-days and pre-transfusion sample from the next scheduled transfusion, adjusted by the duration in days used to calculate the AUC (i.e., between the 15 minutes to 4-hour post-transfusion sample and pre-transfusion sample of the next transfusion) and averaged over all study RCE procedures for each patient.

8.1.1.1 Primary Efficacy Endpoint

For the primary efficacy endpoint, its primary analysis will be conducted in non-bleeding MITT patients who participate in the initial 28-day period and will utilize data from the initial 28-day period and the extension period (if applicable).

Treatment difference in non-bleeding MITT patients will be assessed using a non-inferiority test with a pre-specified non-inferiority margin (15% of the Control mean value), stratified by site. An analysis of variance (ANOVA) model will be used to estimate and test the treatment effects while controlling for the clinical site. Note that non-inferiority will be declared if the lower bound of a 2-sided 95% confidence interval for the mean treatment difference (Test - 0.85 × Control) is greater than or equal to zero.

For the primary efficacy endpoint, the adjusted hemoglobin increment will be averaged over one or more transfusion episodes. An episode-specific hemoglobin increment will be calculated by subtracting the hemoglobin value before each transfusion episode from the hemoglobin value taken 15 minutes to 24 hours post transfusion episode, adjusted by hemoglobin content transfused within the given episode (which may contain multiple RBC components). The hemoglobin content of each transfused RBC component will be calculated using the hemoglobin concentration and post-sample weight of the RBC component (both measured at the blood center), and the percent of the unit transfused (assessed at the hospital). The hemoglobin mass of each transfusion episode is the sum of the hemoglobin content for all RBC components transfused.

The hemoglobin content transfused (g) for a study RBC component will be calculated as:

$$\text{post sampling weight (g)} \div 1.06\ \text{(g/mL)} \times \text{percent of unit transfused} \times \text{hemoglobin concentration (g/mL)} \div 100$$

Non-study RBCs received during the study transfusion period will also be included in the calculation of hemoglobin content transfused. For each non-study RBC component received, the hemoglobin content will be imputed using the average hemoglobin content per study RBC component from the Control group within each

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clinical site.

As exploratory analyses, the treatment difference in the adjusted hemoglobin increment will also be summarized descriptively (with a 95% confidence interval provided) for the following MITT subgroups:

- Repeatedly transfused non-bleeding patients (defined as non-bleeding patients who receive at least 3 study RBC episodes)
- Bleeding patients (defined as patients with active bleeding at baseline)
- Subgroup by clinical site, age group (<18, 18-64, and ≥65 years old), sex, and race (white vs. other races), as appropriate.

8.1.1.2 Secondary Efficacy Endpoint

For the secondary efficacy endpoint of Hb consumption, the analysis will be conducted only in non-bleeding MITT patients who participate in both of the initial 28-day and 6-month extension periods and will utilize integrated data from both periods.

Similar to the primary efficacy endpoint, treatment difference in non-bleeding MITT patients will be assessed using a non-inferiority test with a pre-specified non-inferiority margin (15% of the Control mean value), stratified by site. An analysis of variance (ANOVA) model will be used to estimate the mean treatment differences while controlling for potential confounders including the clinical site. Interaction terms between the treatment and covariates will be explored as necessary. For the adjusted hemoglobin consumption, the upper bound of a two-sided 95% confidence interval for the treatment difference (Test – 1.15 x Control) less than or equal to zero will result in the rejection of inferiority null hypothesis and the conclusion of non-inferiority.

For the secondary efficacy endpoint, the adjusted hemoglobin consumption will be calculated as total hemoglobin mass transfused in grams divided by body weight in kg at baseline and duration of the study transfusion period in days (g/kg/day). The total hemoglobin mass transfused is the sum of the hemoglobin content for all study and non-study RBC components transfused (see calculation given in **Section 8.1.1.2**) during the study transfusion period. Duration of the study transfusion period will be 28 days for the initial acute transfusion period plus 6 months for the extension period option, if applicable, unless patients prematurely discontinue from the study. For patients who prematurely discontinue from the study, their duration of the study

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transfusion period will be calculated as:

$$(\text{end date of study transfusion period}) - (\text{start date of first study RBC component}) + 1$$

where the end date of the study transfusion period will be defined according to the following rules, with Day 1 being the day of the first study RBC component:

- For patients with reasons for withdrawal being death, the death date will be the end date of the study transfusion period (but up to Day 28 for patients not participating in the extension period, and up to the end of additional 6 months for patients participating in the extension period option)
- For patients with reasons for withdrawal other than death (e.g., lost to follow-up, withdrawal of consent, AE), their last date of study or non-study RBC transfusion during the study transfusion period will be the end date of the study transfusion period.

As exploratory analyses, the treatment difference in the adjusted hemoglobin consumption will also be summarized descriptively (with a 95% confidence interval provided) for the following MITT subgroups:

- Repeatedly transfused non-bleeding patients (defined as non-bleeding patients who receive at least 3 study RBC episodes)
- Subgroup by clinical site, age group (<18, 18-64, and ≥65 years old), sex, and race (white vs. other races), as appropriate.

8.1.2 Safety Analyses

8.1.2.1

The primary safety endpoints evaluated in all patients are the proportion of patients with treatment-emergent AEs that are possibly, probably or definitely related to study RBC transfusion through 28 days after the last study transfusion and the proportion of patients with treatment -emergent antibodies with confirmed specificity to IBS RBCs. Only MITT patients will be included in the safety analysis. Treatment-emergent AEs are defined as AEs with an onset date/time that is on or after the start date/time of the first study RBC transfusion. AEs will be summarized by treatment group, system organ class (SOC), and preferred term as applicable. The proportion of patients with AEs possibly, probably, or definitely related to study RBC transfusion will be compared between treatment groups using a CMH test (controlling for clinical site and baseline bleeding status). The relative risk (Test/Control) and

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associated confidence interval will also be reported. In the event of sparse counts, Fisher's exact test may also be used to provide statistical interpretation.

To investigate the potential impact of irradiation, subgroup analysis by irradiation status (yes vs. no) may be presented for the primary efficacy endpoint and selected safety data (including SAEs, AEs, and potassium level). Subgroup analyses by clinical site, age group (<18, 18-64, and ≥65 years old), sex, and race will also be conducted, as appropriate.

Subjects who receive 3 or more IBS RBC transfusion episodes and have an assessment of antibodies after the third study transfusion episode will be summarized as a subgroup representing subjects who are repeatedly exposed to IBS RBC in terms of immunogenicity.

For SCD patients enrolled into the 28-day +6-month extension for three RCE procedures the following assessments will be performed:

- Proportion of subjects with AESI through 28 days after the last study transfusion.
- S-300 and Glutathione (GSH) plasma levels before and 15 minutes to 4 hrs after RCE.

8.2 Determination of Sample Size

The sample size was initially based on clinical consideration with input from the FDA. Approximately 600 transfused patients (300 per arm), bleeding or non-bleeding at baseline, were planned to generate sufficient safety data for the Test and Control components to establish a reasonable estimate of adverse event risk compared to the benefit of IBS RBC.

Subsequent discussion with the Agency resulted in the following additional considerations:

The study will aim to include 468 non-bleeding patients (approximately 234 per treatment group) with evaluable data on the primary efficacy endpoint of adjusted hemoglobin increment. With this sample size, we will have approximately 90% power to declare non-inferiority for the primary efficacy endpoint in non-bleeding patients with a non-inferiority margin of 15% of the control mean at the two-sided 0.05 alpha level, assuming no true treatment difference and a coefficient of variation of 50%.

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The study will also seek to include at least 140 non-bleeding patients requiring repeated transfusions for chronic anemia enrolled into the optional 6-month extension period. Patients who receive 3 or more study transfusion episodes and have an assessment of antibodies after the third study transfusion episode will be summarized as a subgroup representing subjects who are repeatedly exposed in terms of immunogenicity. These patients will contribute to the total non-bleeding patients required for the primary efficacy endpoint.

In addition, up to 30 SCD patients requiring regular repeated RCE will be enrolled into the extension period to allow a total of three consecutive RCE procedures.

It is estimated that between 600 to 800 randomized and transfused patients will be needed in order to meet the targets for sample size to power the primary efficacy endpoint and the 28-day +6-month extension period enrollment goal. The planned sample sizes may not provide adequate power to demonstrate non-inferiority of IBS RBC at the pre-specified non-inferiority margin of 15% of the control mean for the secondary efficacy endpoint of adjusted hemoglobin consumption.

8.3 Interim Safety Analysis

After approximately 300 patients are treated and at any other time that safety or enrollment rate concerns arise, safety data will be summarized in a group blinded manner for the DSMB's interim safety data review. Enrollment and study transfusions will continue during the interim safety evaluation, unless otherwise advised by the DSMB. Depending on the group blinded safety data reviewed, the DSMB may call for an additional unscheduled review, request to see unblinding summary, and/or suggest holding, stopping, or modifying the study for safety concerns.

As this planned interim analysis can only stop the trial for safety concerns, no adjustments will be made for the alpha level. If the study is discontinued as a result of this interim safety review, unblinded safety and efficacy data will be analyzed then and submitted to the DSMB and FDA.

8.4 Criteria for Termination of the Study

No statistical stopping rules will be carried out for this trial. However, specific stopping rules based on slow accrual and/or development of immune reactivity to IBS RBCs will be implemented as described in **Section 7.7**.

The study will be monitored by a DSMB that will examine group-blinded interim safety data as described in **Section** 7.6.

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The Sponsor may stop or pause the trial for any reason; the reason for trial cessation will be documented.

8.5 Procedure for Missing, Unused and Spurious Data

Unless otherwise noted, missing data will be noted as such. For each non-study RBC component received, the hemoglobin content will be imputed as stated in **Section 8.1.1.2.**

8.6 Deviations from the Statistical Plan

Any changes in the planned analyses instituted after commencement of the study will be documented. The reasons for the modifications and when the changes were made will also be documented.

8.7 Selection of Patients to be Analyzed

Unless otherwise specified, analyses will based on the MITT analysis set, including all randomized patients who receive one or more study RBC transfusions during the study transfusion period, and summarized under their assigned treatment group. Randomized patients who receive any study RBC components different from the treatment group assigned may be summarized separately.

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9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Prior to participating in the study, the Investigator agrees to provide Cerus representatives or their designee direct access to source documents for trial-related monitoring and auditing. The quality representative(s) of the Sponsor may visit a clinical facility of blood center to ensure proper conduct of the protocol, recording of data, and maintenance of records.

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10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

During trial conduct, Cerus or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs are accurate. The Investigator and institution will allow Cerus monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Cerus and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.2 Investigational Product

Each red cell collection center and each processing center will be accountable for receipt and disposition of all investigational product inventory shipped to the site. All investigational devices will be stored in a secure area with access limited to authorized study personnel. Inventory records will be maintained and reviewed according to monitoring procedures.

An investigational device receiving and dispensing record will be maintained by the Blood Centers to maintain control of investigational products used during the study. Unused investigational devices must be returned to the Blood Center at the completion of the study or must be destroyed according to standard procedures, per the Sponsor's request.

Any device malfunction occurring during production will be documented on a Device Malfunction Case Report Form in the Electronic Data Capture System. If an investigational device fails to perform in the expected manner at any time, the Sponsor will be notified, and the event will be appropriately reported to Cerus Quality Assurance Group. If a device is received unusable (i.e., unsealed package, broken, etc.), the site will notify the clinical monitor who will contact the Sponsor for further instructions. If requested, defective devices will be returned to the Sponsor for inspection and analysis according to procedures.

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11 ETHICS

11.1 Conduct of the Trial

The trial will be conducted according to the protocol, the International Council on Harmonization E6 Good Clinical Practice (GCP), and applicable local/national regulatory requirements and laws.

11.2 Patient Information and Consent

The informed consent form must be agreed to by Cerus and the IRB/IEC and must be in compliance with ICH GCP, regional regulatory requirements, and legal requirements.

The Investigator must ensure that each trial patient, or his/her legally authorized representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The Investigator will obtain written informed consent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and Cerus before use. The Investigator will retain the original of each patient's signed consent form.

11.3 Institutional Review Board (IRB)/Ethics Committee (EC)

This protocol will be submitted to an appropriate central or local IRB/EC and its written unconditional approval obtained and submitted to Cerus or its designee before enrollment of the first patient.

Cerus will supply relevant data for Investigators to submit to the IRB/EC for the protocol’s review and approval. Written verification of IRB/EC unconditional approval of the protocol and the patient Informed Consent Form (ICF) will be transmitted to Cerus or its designee prior enrolling any patients in the study. This approval must refer to the study by exact protocol title and number (including version), identify documents reviewed, and state the date of approval.

The Investigator must promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risk to human patients or others.

This includes all SAEs that have resulted in an expedited safety report to the regulatory authorities (serious, unexpected AEs possibly related to investigational product).

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Concurrently, the Investigator must send the study Sponsor documentation of such IRB/EC notification. The Investigator must not make any changes in the research without IRB/EC approval and Cerus approval, except where necessary to eliminate apparent immediate hazards to human patients.

11.4 Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files.

However, such medical information may be given to the patient's personal physician, or to other appropriate medical personnel responsible for the patient's welfare.

In addition, data generated as a result of this study are to be available for inspection upon request by local health authority auditors, the Sponsor's monitors, or by the IRB/EC. Therefore, absolute confidentiality cannot be guaranteed.

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12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Cerus and should not be made available in any form to third parties, except for authorized representatives of Cerus or appropriate regulatory authorities, without written permission from Cerus.

It is the Investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

12.2 Record Retention

Investigators/institutions and the Sponsor shall maintain all study records required (by subpart 21CRF 812.140) during the investigation and for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Investigator/institution shall not destroy any such records prior to obtaining written permission from Cerus.

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14 APPENDIXES

14.1 APPENDIX 1: CDC National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol

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National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol

Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

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April 2018



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Version History

Version	Release Date	Summary of Revisions
1.0	March 2009	First version publicly released.
1.1	June 2010	Revised background and text in main body of document.
		Revised case definition criterion based on WG recommendations, pilot responses, and CDC recommendations.
		Updated FNHTR definition to allow reaction without documented fever.
		Defined hypotension for infants and small children
		Clarified TAGVHD probable and possible criteria.
1.2	July 2010	Corrected definition of hypoxemia in glossary of terms.
1.3	June 2011	Added version number and version history summary.
		Summarized introduction and background sections for brevity.
		Reorganized surveillance methods section for ease of use.
		Clarified reporting of "approved deviation" incidents.
		Clarified use of "other" in adverse reaction reporting.
		Clarified use of "doubtful" or "ruled out" in adverse reaction reporting.
		Added denominator summary options to list of available analysis reports.
		Replaced < and > signs with appropriate text for.
		Added "cessation of" to time frame requirements in case definitions.
		NEW probable case definition category for allergic reaction reporting.
		Updated adult hypotensive reaction case definition to align with updated ISBT definition.
		NEW possible imputability category for DHTR.
		DELETED possible case definition category for hypotensive reaction.
		NEW probable imputability category for PTP reaction.
		Updated and clarified imputability categories for TAGVHD reaction.
		DELETED possible case definition category for TRALI.
		Simplified imputability criteria for TTI.
		Clarified case definition and imputability criteria for all adverse reactions.
2.0	January 2013	Complete revision of organization and presentation of information
		Major change in incident reporting requirements. With this release, only incidents that relate to an adverse patient reaction are required for participation.
		Major change in adverse reaction reporting requirements. With this release, minor allergic reactions are no longer required for participation.
		Combined the signs/symptoms with laboratory/radiology columns in case definition tables for clarity. Listed criteria in alphabetical order where possible for consistency and clarity. Moved general severity requirements from the appendix to the criteria tables where they were previously missing.
		Re-ordered adverse reaction tables to put respiratory reactions first.
		Added Imputability criteria of Doubtful, Ruled Out, and Not Determined to the case definition tables as OPTIONAL reporting categories. The reporting is not a change, but including them in the table is new. They were added for clarity.
		Added specific AHTR criteria to allow for reporting of non-immune mediated reactions.
		Added a separate case definition table for Other and Unknown reactions. These categories are available for OPTONAL use.
		Removed redundant and unnecessary appendices.
2.1	August 2013	Minor revisions to verbiage throughout for clarity.
		Added definitions and illustration of surveillance key terms in Section 1.
		Added clarification of surveillance vs. clinical definitions in Section 1.
		Added less-specific case definition categories for OPTIONAL reporting of cases that do not fully meet CDC case criteria for the following reactions: hypotension, febrile non-hemolytic, acute hemolytic and delayed hemolytic.

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Version	Release Date	Summary of Revisions
		Added a possible case definition category for TTI for OPTIONAL reporting of syndromic cases that are not laboratory confirmed.
2.1.1	September 2013	Updated diagram in Section 1 and added version history for v2.0 and v2.1.
2.1.2	January 2014	Updated the incident codes in Section 4 and included required reporting of discards and total crossmatch procedures on the Monthly Reporting Denominators form in Section 5.
2.1.3	August 2014	Added a suggested citation for the surveillance protocol in Section 1. Updated the acute hemolytic case definition in Section 3 for clarity. Updated the reporting requirements in Section 5 for clarity.
2.2	January 2016	Updated contact instructions for consistency in Section 1: User support
		Updated version number in Section 1: Suggested Citation
		Remove Root Cause Analysis Result from Section 4: Incident Glossary
		Updated denominator report description to include Pathogen-reduced products in Section 5: Required Reporting
2.3	June 2016	Updated denominator report description to include Table 3 description.
2.4	January 2017	Section 1: Setting – Added additional Annual Facility form for Non-Acute Care Facilities to report.
		Section 2: Annual Facility Survey – Added information about Non-Acute Care Facility Annual Facility Survey, Added links to the Annual Facility Survey – Non-Acute Care Facility form and table of instructions for clarity.
2.5	January 2018	Section 1: Training, User Support, Data Reporting – Minor language changes for clarification
		Section 3: Adverse Reaction Classification – Added information about module-generated classification designations.
		Adverse Reaction Glossary: Updated the definition of fever to be consistent with FNHTR criteria.
2.5.2.	April 2018	Section 4: Incident codes - UT 06 – "incompatible" replaced with "unapproved"

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Section 1. Hemovigilance Module Surveillance Overview

Purpose
The National Healthcare Safety Network (NHSN) Hemovigilance (HV) Module was created to implement national surveillance of transfusion-associated adverse events aimed at improving patient safety, minimizing morbidity and mortality of transfusion recipients, and identifying emerging complications and pathogens associated with blood transfusion.

Settings
The Hemovigilance Module may be used by any U.S. healthcare facility where blood components and manufactured blood products are transfused (e.g., adult or pediatric facilities, acute or non-acute care facilities). Surveillance must be performed facility-wide, including patient care areas for emergency, general medical, and surgical patients; obstetrics and gynecology; orthopedics, oncology, and other chronic diseases; and any other facility location where transfusions are administered.

Methods
The NHSN Hemovigilance Module requires comprehensive surveillance of patients and blood components throughout the transfusion process, from product receipt to administration to the patient. Participation in the NHSN Hemovigilance Module requires reporting of all adverse transfusion reactions and reaction-associated incidents that occur **for patients transfused at or by your facility** as well as a monthly summary of components transfused or discarded and patient samples collected for type and screen or crossmatch.

Data Collection
NHSN is a web-based application used by healthcare facilities to report surveillance data. Paper versions of all forms are used to collect data prior to data entry in the NHSN Hemovigilance Module. The paper forms are available on the NHSN Blood Safety Surveillance website. A link to the appropriate form(s) and their instructions is provided in the following sections for your convenience.

Training
Training presentations are available on the NHSN Blood Safety Surveillance website for self-paced training and must be reviewed prior to participating in the Hemovigilance Module. CDC also provides webinar and in-person training opportunities for current NHSN participants. These opportunities are communicated through the NHSN quarterly newsletter and emails from the Hemovigilance Team.

User Support
CDC is available to answer your questions about the Surveillance Protocol and to help navigate the NHSN web application. Please contact us at nhsn@cdc.gov. Type **HEMOVIGILANCE** in the subject line for quickest routing to the Hemovigilance Team.

Suggested Citation for the Hemovigilance Module Surveillance Protocol
U.S. Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Manual: Biovigilance Component v2.5. Atlanta, GA: Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases. Available at: http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf. Accessed [enter date].

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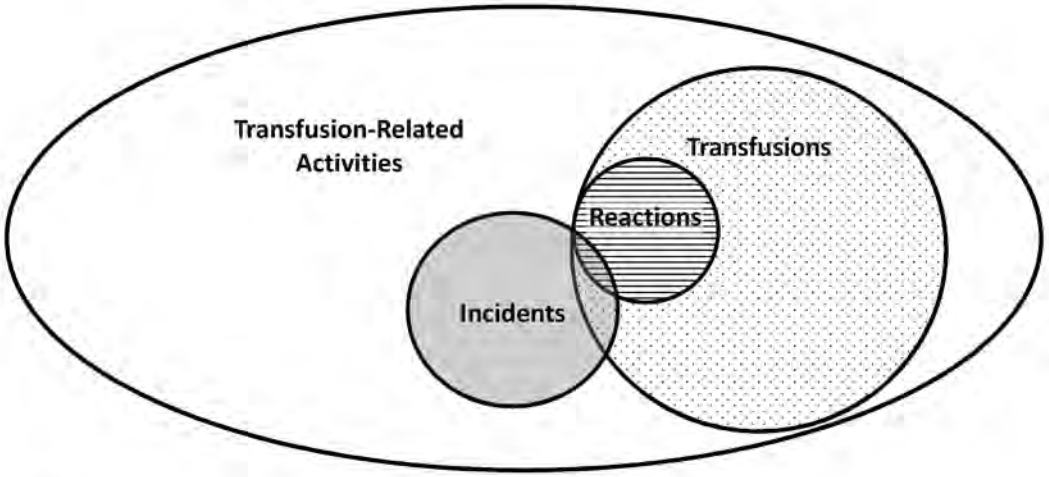
Key Terms (see Fig. 1)

- **Adverse event:** An unintended and undesirable occurrence before, during or after transfusion of blood or blood components. Adverse events include both incidents and adverse reactions.
- **Adverse reaction:** An undesirable response or effect in a patient temporally associated with the administration of blood or blood components. It may or may not be the result of an incident.
- **Incident:** Any error or accident that could affect the quality or efficacy of blood, blood components, or patient transfusions. It may or may not result in an adverse reaction in a transfusion recipient.
- **Near miss:** A subset of incidents that are discovered before the start of a transfusion that *could* have led to a wrongful transfusion or an adverse reaction in a transfusion recipient.

Data Reporting (See Fig. 1)

- An annual facility demographic and practice survey for each **calendar** year of participation
- ALL adverse reactions defined in this protocol that follow transfusion **at or by your facility**
- ALL incidents (i.e., errors or accidents) associated with an adverse reaction
- The number of blood components transfused or discarded and patient samples collected for type and screen or crossmatch each month

Figure 1. Venn diagram of NHSN Hemovigilance Module surveillance terms.



Transfusion-Related Activities
- Patient Sample Collection
- Sample Handling and Testing
- Inventory Management
- Patient Monitoring

Transfusion
- Number of Components
- Number of Patients

Adverse Events

Reactions

Incidents

Near Miss Incidents

Incidents Related to Transfusion (No Adverse Reaction)

Incidents Related to Transfusion and Adverse Reaction

NHSN National Healthcare Safety Network

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Section 2. Hemovigilance Module Annual Facility Survey

Required Reporting
Participating facilities must enter the Hemovigilance Module Annual Facility Survey at the time that they enroll or activate the Biovigilance Component and at the beginning of each calendar year thereafter. The survey is used by CDC to classify facilities for appropriate comparisons in aggregate data analyses and to learn more about common practices among transfusion services. The data collected in the survey covers the previous **calendar** year. For example, if the facility is enrolling in NHSN for the first time in October of 2013, report information for January 2012-December 2012 on the first Hemovigilance Module Annual Facility Survey. In January 2014, complete a new survey with data from January 2013-December 2013. CDC recommends collecting all survey information on a paper form before attempting to enter data into the web application.

As of January 2017, non-acute care facilities are able to report hemovigilance data to NHSN. Non-acute care facilities should complete Annual Facility Survey for Non-acute care facility 57.306. This form contains questions tailored to non-acute care facilities. Users may refer to the Non-Acute Care Facility Table of Instructions form 57.306 for detailed instruction about data collection.

Form
CDC 57.300 Hemovigilance Module Annual Facility Survey - Acute Care Facility

CDC 57.306 Hemovigilance Module Annual Facility Survey - Non-Acute Care Facility

Form Instructions
CDC 57.300 Hemovigilance Module Annual Facility Survey - Acute Care Facility Table of Instructions

CDC 57.306 Hemovigilance Module Annual Facility Survey - Non-Acute Care Facility Table of Instructions

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Section 3: Hemovigilance Module Adverse Reactions

Required Reporting
All CDC-defined transfusion-associated adverse reactions that are possibly, probably, or definitely related to a **transfusion performed by the participating facility** must be reported to NHSN. If a patient experiences more than one adverse reaction during or following the same transfusion episode, complete a separate form for each reaction. Adverse reaction reports should be entered into NHSN after an investigation of the reaction has been completed and imputability has been determined to the extent possible. Reports should be entered within 30 days of the month that the reaction occurred or when the investigation is completed.

Optional Reporting
Reporting suspected adverse reactions where imputability is determined to be doubtful or ruled out is not required. A facility may report reactions determined to be doubtful or ruled out in order to use NHSN to document transfusion reaction investigations each month. Adverse reactions that are not defined in the surveillance protocol may also be reported using the 'Other' and 'Unknown' adverse reaction categories; standard severity and imputability criteria are provided for that purpose.

Adverse Reaction Classification
Each CDC-defined transfusion-associated adverse reaction **must** be classified according to the reaction-specific case definition, severity, and imputability criteria printed in the protocol. It is imperative that every facility classify adverse reactions according to protocol definitions. Accurate classification will usually require a detailed review of the patient record.

To assist in classification, the Module will generate and assign designations for case definition, severity, and imputability based on signs, symptoms, and lab results entered in the investigation results section of the adverse reaction form.

Surveillance definitions are distinctly different from clinical definitions. Surveillance definitions are designed to capture data consistently and reliably in order to identify trends and inform quality improvement practices. The surveillance definitions are not intended as clinical diagnostic criteria or to provide treatment guidance.

Defined Adverse Reactions
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated dyspnea (TAD)
- Allergic reaction (where severity is severe, life threatening, or death)
- Hypotensive transfusion reaction
- Febrile non-hemolytic transfusion reaction (FNHTR)
- Acute hemolytic transfusion reaction (AHTR)
- Delayed hemolytic transfusion reaction (DHTR)
- Delayed serologic transfusion reaction (DSTR)
- Transfusion-associated graft vs. host disease (TAGVHD)
- Post-transfusion purpura (PTP)
- Transfusion-transmitted infection (TTI)

Form
Adverse reaction forms are available at the NHSN Blood Safety Surveillance website.

Form Instructions
Adverse Reaction forms' Table of Instructions are available at the NHSN Blood Safety Surveillance website.

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Adverse Reaction Case Classification Criteria Tables

Transfusion-associated circulatory overload (TACO)

Case Definition	Severity	Imputability
Definitive: New onset or exacerbation of 3 or more of the following within 6 hours of cessation of transfusion: • Acute respiratory distress (dyspnea, orthopnea, cough) • Elevated brain natriuretic peptide (BNP) • Elevated central venous pressure (CVP) • Evidence of left heart failure • Evidence of positive fluid balance • Radiographic evidence of pulmonary edema **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** No other explanations for circulatory overload are possible. **Probable:** Transfusion is a likely contributor to circulatory overload **AND EITHER** The patient received other fluids as well **OR** The patient has a history of cardiac insufficiency that could explain the circulatory overload, but transfusion is just as likely to have caused the circulatory overload. **Possible:** The patient has a history of pre-existing cardiac insufficiency that most likely explains circulatory overload. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Transfusion-related acute lung injury (TRALI)

Case Definition	Severity	Imputability
Definitive: NO evidence of acute lung injury (ALI) prior to transfusion **AND** ALI onset during or within 6 hours of cessation of transfusion **AND** Hypoxemia defined by any of these methods: • PaO2/FiO2 less than or equal to 300 mm Hg • Oxygen saturation less than 90% on room air • Other clinical evidence **AND** Radiographic evidence of bilateral infiltrates **AND** No evidence of left atrial hypertension (i.e., circulatory overload) **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** There are no alternative risk factors for ALI present. **Probable:** N/A **Possible:** There is evidence of other causes for acute lung injury such as: Direct Lung Injury • Aspiration • Pneumonia • Toxic inhalation • Lung contusion • Near drowning Indirect Lung Injury • Severe sepsis • Shock • Multiple trauma • Burn injury • Acute pancreatitis • Cardiopulmonary bypass • Drug overdose **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Transfusion-associated dyspnea (TAD)

Case Definition	Severity	Imputability
Definitive: Acute respiratory distress occurring within 24 hours of cessation of transfusion **AND** Allergic reaction, TACO, and TRALI definitions are not applicable. **Probable:** N/A **Possible:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Patient has no other conditions that could explain symptoms. **Probable:** There are other potential causes that could explain symptoms, but transfusion is the most likely cause. **Possible:** Other present causes are most likely, but transfusion cannot be ruled out. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Allergic reaction

Note: Minor allergic reactions (Non-severe) do not have to be reported to NHSN.

Case Definition	Severity	Imputability
Definitive: **2 or more** of the following occurring during or within 4 hours of cessation of transfusion: • Conjunctival edema • Edema of lips, tongue and uvula • Erythema and edema of the periorbital area • Generalized flushing • Hypotension • Localized angioedema • Maculopapular rash • Pruritus (itching) • Respiratory distress: bronchospasm • Urticaria (hives) **Probable:** **ANY 1** of the following occurring during or within 4 hours of cessation of transfusion: • Conjunctival edema • Edema of lips, tongue and uvula • Erythema and edema of the periorbital area • Localized angioedema • Maculopapular rash • Pruritus (itching) • Urticaria (hives)	**Severe, Life-threatening, Death:** Involves respiratory and/or cardiovascular systems and presents like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous symptoms, there are airway symptoms, hypotension, or associated symptoms like hypotonia and syncope. The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing, bronchospasm, hypoxemia). Such a reaction usually occurs during or shortly after cessation of transfusion. **Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Occurs during or within 2 hours of cessation of transfusion **AND** No other evidence of environmental, drug or dietary risks. **Probable:** Occurs during or within 2 hours of cessation of transfusion **AND** There are other potential causes present that could explain symptoms, but transfusion is the most likely cause. **Possible:** Occurs 2 - 4 hours after cessation of transfusion **OR** Other present causes are most likely, but transfusion cannot be ruled out.
OPTIONAL	**OPTIONAL**	**OPTIONAL**
Possible: N/A	**Non-severe:** There is no immediate risk to the life of the patient, and the patient responds quickly to symptomatic treatment.	**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Hypotensive transfusion reaction

Case Definition	Severity	Imputability
Definitive: All other adverse reactions presenting with hypotension are excluded **AND** Hypotension occurs during or within 1 hour after cessation of transfusion. • **Adults (18 years and older):** Drop in systolic BP of greater than or equal to 30 mmHg and systolic BP less than or equal to 80 mmHg. • **Infants, children and adolescents (1 year to less than 18 years old):** Greater than 25% drop in systolic BP from baseline (e.g., drop in systolic BP of 120mmHg to below 90mmHg). • **Neonates and small infants (less than 1 year old OR any age and less than 12 kg body weight):** Greater than 25% drop in baseline value using whichever measurement is being recorded (e.g., mean BP). **Probable:** N/A	**Non-severe:** The recipient required no more than discontinuation of transfusion and symptom management and no long-term morbidity resulted from the reaction. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to hypotension, or hypotension led directly to long-term morbidity (e.g., brain damage) **AND** Vasopressors were not required. **Life-threatening:** The recipient required vasopressors. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Occurs less than 15 minutes after the start of the transfusion **AND** Responds rapidly (i.e., within 10 minutes) to cessation of transfusion and supportive treatment **AND** The patient has no other conditions that could explain hypotension. **Probable:** Onset is between 15 minutes after start and 1 hour after cessation of transfusion **OR** The patient does not respond rapidly to cessation of transfusion and supportive treatment **OR** There are other potential causes present that could explain hypotension, but transfusion is the most likely cause. **Possible:** Other conditions that could readily explain hypotension are present.
OPTIONAL		**OPTIONAL**
Possible: Hypotension occurs, does not meet the criteria above. Other, more specific reaction definitions do not apply.		**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Febrile non-hemolytic transfusion reaction (FNHTR)
Note: Reactions may be classified as FNHTRs in the absence of fever if chills or rigors occur.

Case Definition	Severity	Imputability
Definitive: Occurs during or within 4 hours of cessation of transfusion **AND EITHER** Fever (greater than or equal to 38°C/100.4°F oral and a change of at least 1°C/1.8°F) from pre-transfusion value **OR** Chills/rigors are present. **Probable:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.	**Definite:** Patient has no other conditions that could explain signs/symptoms. **Probable:** There are other potential causes present that could explain signs/symptoms, but transfusion is the most likely cause. **Possible:** Other present causes are most likely, but transfusion cannot be ruled out.
OPTIONAL		**OPTIONAL**
Possible: FNHTR is suspected, but reported symptoms and/or available information are not sufficient to meet the criteria defined above. Other, more specific adverse reaction definitions do not apply.	**Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Acute hemolytic transfusion reaction (AHTR)

Note: Report hemolytic reactions resulting from immune or non-immune causes, including when the recipient is **intentionally** transfused with incompatible blood components.

Case Definition	Severity	Imputability
Definitive: Occurs during, or within 24 hours of cessation of transfusion with new onset of **ANY** of the following signs/symptoms: • Back/flank pain • Chills/rigors • Disseminated intravascular coagulation (DIC) • Epistaxis • Fever • Hematuria (gross visual hemolysis) • Hypotension • Oliguria/anuria • Pain and/or oozing at IV site • Renal failure **AND** **2** or more of the following: • Decreased fibrinogen • Decreased haptoglobin • Elevated bilirubin • Elevated LDH • Hemoglobinemia • Hemoglobinuria • Plasma discoloration c/w hemolysis • Spherocytes on blood film **AND EITHER** **(IMMUNE-MEDIATED)** Positive direct antiglobulin test (DAT) for anti-IgG or anti-C3 **AND** Positive elution test with alloantibody present on the transfused red blood cells **OR** **(NON-IMMUNE MEDIATED)** Serologic testing is negative, and physical cause (e.g., thermal, osmotic, mechanical, chemical) is confirmed. **Probable:** Meets signs and symptoms criteria for acute hemolysis **AND EITHER** **(IMMUNE MEDIATED)** Physical cause is excluded but serologic evidence is not sufficient to meet definitive criteria **OR** **(NON-IMMUNE MEDIATED)** Physical cause is suspected and serologic testing is negative. **OPTIONAL** **Possible:** AHTR is suspected within 24 hours of cessation of transfusion, but symptoms, test results, and/or information are not sufficient to meet the criteria defined above. Other, more specific adverse definitions do not apply.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly, probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** ABO or other allotypic RBC antigen incompatibility is known **OR** Only transfusion-related (i.e., immune or non-immune) cause of acute hemolysis is present. **Probable:** There are other potential causes present that could explain acute hemolysis, but transfusion is the most likely cause. **Possible:** Other causes of acute hemolysis are more likely, but transfusion cannot be ruled out. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Delayed hemolytic transfusion reaction (DHTR)

Note: Report all hemolytic reactions, including when the recipient is **intentionally** transfused with incompatible blood components.

Case Definition	Severity	Imputability
Definitive: Positive direct antiglobulin test (DAT) for antibodies developed between 24 hours and 28 days after cessation of transfusion **AND EITHER** Positive elution test with alloantibody present on the transfused red blood cells **OR** Newly-identified red blood cell alloantibody in recipient serum **AND EITHER** Inadequate rise of post-transfusion hemoglobin level or rapid fall in hemoglobin back to pre-transfusion levels **OR** Otherwise unexplained appearance of spherocytes. **Probable:** Newly-identified red blood cell alloantibody demonstrated between 24 hours and 28 days after cessation of transfusion **BUT** Incomplete laboratory evidence to meet definitive case definition criteria. **NOTE:** Patient may be asymptomatic or have symptoms that are similar to but milder than AHTR; symptoms are not required to meet case definition criteria.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** No other explanation for symptoms or newly-identified antibody is present. **Probable:** An alternate explanation for symptoms or newly-identified antibody is present, but transfusion is the most likely cause. **Possible:** Other explanations for symptoms or newly-identified antibody are more likely, but transfusion cannot be ruled out.
OPTIONAL		**OPTIONAL**
Possible: DHTR is suspected, but reported symptoms, test results, and/or available information are not sufficient to meet the criteria defined above. Other, more specific adverse reaction definitions do not apply.		**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Delayed serologic transfusion reaction (DSTR)

Note: Delayed serologic reactions should only be reported for patients **transfused by your facility**.

Case Definition	Severity	Imputability
Definitive: Absence of clinical signs of hemolysis **AND** Demonstration of new, clinically-significant antibodies against red blood cells **BY EITHER** Positive direct antiglobulin test (DAT) **OR** Positive antibody screen with newly identified RBC alloantibody. **Probable:** N/A **Possible:** N/A	**Not Determined:** Since this is by definition a reaction with no clinical symptoms, severity of the reaction cannot be graded.	**Definite:** New alloantibody is identified between 24 hours and 28 days after cessation of transfusion **AND** Transfusion performed by your facility is the only possible cause for seroconversion. **Probable:** New alloantibody is identified between 24 hours and 28 days after cessation of transfusion **AND** The patient has other exposures (e.g. transfusion by another facility or pregnancy) that could explain seroconversion, but transfusion by your facility is the most likely cause. **Possible:** New alloantibody is identified between 24 hours and 28 days after cessation of transfusion **AND** The patient was transfused by your facility, but other exposures are present that most likely explain seroconversion. **OPTIONAL** **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Transfusion-associated graft vs. host disease (TAGVHD)

Case Definition	Severity	Imputability
Definitive: A clinical syndrome occurring from 2 days to 6 weeks after cessation of transfusion characterized by: • Characteristic rash: erythematous, maculopapular eruption centrally that spreads to extremities and may, in severe cases, progress to generalized erythroderma and hemorrhagic bullous formation. • Diarrhea • Fever • Hepatomegaly • Liver dysfunction (i.e., elevated ALT, AST, Alkaline phosphatase, and bilirubin) • Marrow aplasia • Pancytopenia **AND** Characteristic histological appearance of skin or liver biopsy. **Probable:** Meets definitive criteria **EXCEPT** Biopsy negative or not done. **Possible:** N/A	**Non-severe:** N/A **Severe:** Patient had marked symptoms and responded to treatment. **Life-threatening:** Patient had severe symptoms and required life-saving treatment (e.g., immunosuppression). **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** WBC chimerism present in the absence of alternative diagnoses. **Probable:** WBC chimerism present **BUT** Other potential causes are present (e.g., stem cell transplantation). **Possible:** WBC chimerism not present or not done **OR** Alternative explanations are more likely (e.g., solid organ transplantation). OPTIONAL **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Post transfusion purpura (PTP)

Case Definition	Severity	Imputability
Definitive: Alloantibodies in the patient directed against HPA or other platelet specific antigen detected at or after development of thrombocytopenia **AND** Thrombocytopenia (i.e., decrease in platelets to less than 20% of pre-transfusion count). **Probable:** Alloantibodies in the patient directed against HPA or other platelet specific antigen detected at or after development of thrombocytopenia. **AND** Decrease in platelets to levels between 20% and 80% of pre-transfusion count.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Occurs 5-12 days post-transfusion **AND** Patient has no other conditions to explain thrombocytopenia. **Probable:** Occurs less than 5 or more than 12 days post-transfusion **OR** There are other potential causes present that could explain thrombocytopenia, but transfusion is the most likely cause. **Possible:** Alternate explanations for thrombocytopenia are more likely, but transfusion cannot be ruled out.
OPTIONAL		**OPTIONAL**
Possible: PTP is suspected, but laboratory findings and/or information are not sufficient to meet defined criteria above. For example, the patient has a drop in platelet count to less than 80% of pre-transfusion count but HPA antibodies were not tested or were negative. Other, more specific adverse reaction definitions do not apply.		**Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Transfusion-transmitted infection (TTI)

Case Definition	Severity	Imputability
Definitive: Laboratory evidence of a pathogen in the transfusion recipient. **Probable:** N/A	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function.	**Definite:** **ONE or more of the following:** • Evidence of the pathogen in the transfused component • Evidence of the pathogen in the donor at the time of donation • Evidence of the pathogen in an additional component from the same donation • Evidence of the pathogen in an additional recipient of a component from the same donation **AND** No other potential exposures to the pathogen could be identified in the recipient. **AND EITHER** Evidence that the recipient was not infected with the pathogen prior to transfusion **OR** Evidence that the identified pathogen strains are related by molecular or extended phenotypic comparison testing with statistical confidence ($p<0.05$). **Probable:** **ONE or more of the following:** • Evidence of the pathogen in the transfused component • Evidence of the pathogen in the donor at the time of donation • Evidence of the pathogen in an additional component from the same donation • Evidence of the pathogen in an additional recipient of a component from the same donation. **AND EITHER:** Evidence that the recipient was not infected with this pathogen prior to transfusion **OR** No other potential exposures to the pathogen could be identified in the recipient. **Possible:** Case fails to meet definite, probable, doubtful, or ruled out imputability criteria.
OPTIONAL		**OPTIONAL**
Possible: Temporally associated unexplained clinical **illness** consistent with infection, but no pathogen is detected in the recipient. Other, more specific adverse reactions are ruled out. **Note:** Possible cases cannot meet the **definite** or **probable** imputability criteria.	**Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction.** **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Doubtful:** Laboratory evidence that the recipient was infected with this pathogen prior to transfusion **OR** Evidence is clearly in favor of a cause other than transfusion, but transfusion cannot be excluded. **Ruled Out:** **ALL** of the following (where applicable): • Evidence that the transfused component was negative for this pathogen at the time of transfusion • Evidence that the donor was negative for this pathogen at the time of donation • Evidence that additional components from the same donation were negative for this pathogen **OR** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Transfusion-transmitted infection (TTI)
(continued)

Pathogens of well-documented importance in blood safety.

These pathogens have public health significance for hemovigilance, are well-documented blood stream pathogens, and/or are routinely screened for in blood donors. A full list of potentially infectious organisms is available in the drop-down pathogen list in NHSN.

Bacterial	Viral	Parasitic	Other
Enterobacter cloacae *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Staphylococcus epidermidis* *Staphylococcus lugdunensis* Syphilis (*Treponema pallidum*) *Yersinia enterocolitica*	Cytomegalovirus (CMV) *Enterovirus spp.* Epstein Barr (EBV) Hepatitis A Hepatitis B Hepatitis C Human Immunodeficiency Virus 1 (HIV-1) Human Immunodeficiency Virus 2 (HIV-2) Human Parvovirus B-19 Human T-Cell Lymphotropic Virus-1 (HTLV-1) Human T-Cell Lymphotropic Virus-2 (HTLV-2) West Nile Virus (WNV) Zika Virus (ZIKAVI)	Babesiosis (*Babesia spp.*) Chagas disease (*Trypanosoma cruzi*) Malaria (*Plasmodium spp.*)	Creutzfeldt-Jakob Disease, Variant (vCJD)

Investigation triggers for potential transfusion-transmitted infections:

1. Identification by testing (e.g., gram stain, other smear/staining, culture, or other method) of a bacterial, mycobacterial, or fungal pathogen in a recipient within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected pathogen.

2. Identification of an unexpected virus in the transfusion recipient by testing (e.g., culture, direct fluorescent antibody, or polymerase chain reaction) within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected virus.

3. Identification of an unexpected parasite in the recipient by testing (e.g., blood smear, histopathology, serologic testing, or polymerase chain reaction) within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected parasite.

4. Any of the above laboratory findings in the recipient unit upon residual testing.

5. Unexplained clinical events occurring after transfusion that are consistent with transfusion-transmitted infection, such as:
   a. Encephalitis, meningitis, or other unexplained central nervous system abnormalities.
   b. Sepsis with or without multi-organ system dysfunction.
   c. Hemolytic anemia and/or fever (e.g., in cases of transfusion-associated babesiosis or malaria).
   d. Recipient death.

6. For pathogens routinely screened in the blood donor, any infection in the recipient occurring within 6 months after transfusion if:
   a. The index donation testing was negative but
   b. The donor was subsequently found to be infected, and
   c. The recipient had no pre-transfusion history of the same infection.

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Other or Unknown

Other: Use this option if the recipient experienced an adverse reaction that is not defined in the Hemovigilance Module surveillance protocol (e.g., transfusion-associated acute gut injury (TRAGI), transfusion-associated immunomodulation (TRIM), iron overload, microchimerism, hyperkalemia, thrombosis).

Unknown: Use this category if the patient experienced transfusion-related symptoms, but the medical event that caused those symptoms could not be classified.

Note: Reporting 'Other' and 'Unknown' reactions is not required by CDC.

REPORTING OPTIONAL		
Case Definition	**Severity**	**Imputability**
Not Applicable: CDC does not specifically define the 'Other' or 'Unknown' adverse reaction categories, therefore the case definition criteria may only be reported as N/A.	**Non-severe:** Medical intervention (e.g. symptomatic treatment) is required but lack of such would not result in permanent damage or impairment of a bodily function. **Severe:** Inpatient hospitalization or prolongation of hospitalization is directly attributable to the adverse reaction, persistent or significant disability or incapacity of the patient occurs as a result of the reaction, or a medical or surgical intervention is necessary to preclude permanent damage or impairment of a body function. **Life-threatening:** Major intervention required following the transfusion (e.g. vasopressors, intubation, transfer to intensive care) to prevent death. **Death:** The recipient died **as a result of the adverse transfusion reaction. Death** should be used if death is **possibly**, **probably** or **definitely** related to transfusion. If the patient died of a cause other than the transfusion, the severity of the reaction should be graded as appropriate given the clinical circumstances related to the reaction. **Not Determined:** The severity of the adverse reaction is unknown or not stated.	**Definite:** Conclusive evidence exists that the adverse reaction can be attributed to the transfusion. **Probable:** Evidence is clearly in favor of attributing the adverse reaction to the transfusion. **Possible:** Evidence is indeterminate for attributing the adverse reaction to the transfusion or an alternate cause. **Doubtful:** Evidence is clearly in favor of a cause other than the transfusion, but transfusion cannot be excluded. **Ruled Out:** There is conclusive evidence beyond reasonable doubt of a cause other than the transfusion. **Not Determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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Adverse Reaction Glossary

Antibodies often associated with AHTR, DHTR, DSTR:

Anti-A	Anti-B	Anti-A,B	Anti-C	Anti-c	Anti-D	Anti-E	Anti-e	Anti-Fy^a
Anti-Fy^b	Anti-Jk^a	Anti-Jk^b	Anti-K	Anti-k	Anti-M	Anti-S	Other	

Bronchospasm (wheezing): A contraction of smooth muscle in the walls of the bronchi and bronchioles, causing acute narrowing and obstruction of the respiratory airway. This constriction can result in a rasp or whistling sound while breathing.

Chills/rigors: A feeling of cold with shivering or shaking and pallor.

Disseminated intravascular coagulation (DIC): Bleeding disorder characterized by reduction in the factors involved in blood clotting due to their use in widespread clotting within the vessels. The intravascular clotting ultimately produces hemorrhage because of rapid consumption of clotting factors.

Edema: Swelling of soft tissues as a result of excessive fluid accumulation.

Epistaxis: Bleeding from the nose.

Fever: For the purposes of hemovigilance, greater than or equal to 38 °C/100.4 °F oral and a change of at least 1 °C/1.8 °F from pre-transfusion value.

Hematuria: Presence of blood or red blood cells in the urine.

Hemoglobinemia: The presence of free hemoglobin in the blood plasma.

Hemoglobinuria: Presence of free hemoglobin in the urine.

Hypoxemia: Abnormal deficiency in the concentration of oxygen in arterial blood. PaO2 / FiO2 less than or equal to 300 mm Hg OR oxygen saturation is less than 90% on room air.

Jaundice: New onset or worsening of yellow discoloration (icterus) of the skin or sclera (scleral icterus) secondary to an increased level of bilirubin.

Oliguria: New onset of decreased urinary output (less than 500cc output per 24 hours).

Other rash: Non-urticarial skin rash.

Pruritus: Itching.

Shock: A drop in blood pressure accompanied by a drop in cardiac output including rapid heart rate (increase to 100 beats per minute or more), rapid breathing, cutaneous vasoconstriction, pallor, sweating, decreased or scanty urine production, agitation and/or loss of consciousness that required fluid resuscitation, with or without inotropic support.

Shortness of breath (dyspnea): New onset or significant worsening of shortness of breath; or a significant increase in respiratory rate (with or without hypoxemia).

Urticaria (hives): Raised wheals on the skin.

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Section 4. Hemovigilance Module Incidents

Required Reporting
All incidents (i.e., accidents or errors) that are **associated with a reported adverse reaction** must be reported to NHSN using a detailed Incident form (CDC 57.305). If multiple incidents occur in association with an adverse reaction then report all. Incidents may occur before (e.g., wrong product released) or after (e.g., failure to report adverse reaction to blood bank) an adverse reaction. Each reaction must be reported using the detailed incident form; the incident result must be coded as 'Product transfused, reaction' to enter the associated patient identifier on the form. After the incident record is entered, the adverse reaction record must be linked to the incident record in the NHSN web application.

Incident Classification
Use the incident codes provided at the end of this section to classify incidents. If there is uncertainty then please contact NHSN User Support.

Optional Reporting
Any incident may be optionally reported to NHSN using the detailed Incident form (57.305) or the Monthly Incident Summary form (57.302). Approved deviations from standard operating procedure are not considered incidents because they did not occur by accident or in error. However, approved deviations may be optionally reported for a facility's use. Incidents that are optionally reported will not be aggregated or analyzed by CDC.

Form
CDC 57.305 Hemovigilance Module Incident

Form Instructions
CDC 57.305 Hemovigilance Module Incident Table of Instructions

Summary Form (Optional)
CDC 57.302 Hemovigilance Module Monthly Incident Summary

Summary Form Instructions (Optional)
CDC 57.302 Hemovigilance Module Monthly Incident Summary Table of Instructions

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Incident Codes

Note: Incident codes are based on MERS TM (US) and TESS (Canada) incident classification schemes.

Product Check-In
(Transfusion Service)
Events that occur during the shipment and receipt of products into the transfusion service from the supplier, another hospital site, satellite storage, or clinical area.
- PC 00 Detail not specified
- PC 01 Data entry incomplete/incorrect/not performed
- PC 02 Shipment incomplete/incorrect
- PC 03 Products and paperwork do not match
- PC 04 Shipped/transported under inappropriate conditions
- PC 05 Inappropriate return to inventory
- PC 06 Product confirmation incorrect/not performed
- PC 07 Administrative check not incorrect/not performed (record review/audit)
- PC 08 Product label incorrect/missing

Product Storage
(Transfusion Service)
Events that occur during product storage by the transfusion service.
- US 00 Detail not specified
- US 01 Incorrect storage conditions
- US 03 Inappropriate monitoring of storage device
- US 04 Unit stored on incorrect shelf (e.g., ABO/autologous s/directed)
- US 05 Incorrect storage location

Inventory Management
(Transfusion Service)
Events that involve quality management of the blood product inventory.
- IM 00 Detail not specified
- IM 01 Inventory audit incorrect/not performed
- IM 02 Product status incorrectly/not updated online (e.g., available/discarded)
- IM 03 Supplier recall/traceback not appropriately addressed/not performed
- IM 04 Product order incorrectly/not submitted to supplier
- IM 05 Outdated product in available inventory
- IM 06 Recalled/quarantined product in available inventory

Product/Test Request
(Clinical Service)
Events that occur when the clinical service orders patient tests or blood products for transfusion.
- PR 00 Detail not specified
- PR 01 Order for wrong patient
- PR 02 Order incompletely/incorrectly ordered (online order entry)
- PR 03 Special processing needs not indicated (e.g., CMV negative, autologous)
- PR 04 Order not done
- PR 05 Inappropriate/unnecessary (intended) test ordered
- PR 06 Inappropriate/unnecessary (intended) blood product ordered
- PR 07 Incorrect (unintended) test ordered
- PR 08 Incorrect (unintended) blood product ordered

Product/Test Order Entry
(Transfusion Service)
Events that occur when the transfusion service receives a patient order. This process may be excluded if clinical service uses online ordering.
- OE 00 Detail not specified
- OE 01 Order entered for wrong patient
- OE 02 Order incompletely/incorrectly entered online
- OE 03 Special processing needs not entered (e.g., CMV-, autologous)
- OE 04 Order entry not done
- OE 05 Inappropriate/unnecessary (intended) test order entered
- OE 06 Inappropriate/unnecessary (intended) blood product order entered
- OE 07 Incorrect (unintended) test ordered
- OE 08 Incorrect (unintended) blood product ordered

Sample Collection
(Service collecting the samples)
Events that occur during patient sample collection.
- SC 00 Detail not specified
- SC 01 Sample labeled with incorrect patient name
- SC 02 Not labeled
- SC 03 Wrong patient collected
- SC 04 Collected in wrong tube type
- SC 05 Sample QNS
- SC 06 Sample hemolyzed
- SC 07 Label incomplete/illegible/incorrect (other than patient name)
- SC 08 Sample collected in error
- SC 09 Requisition arrived without samples
- SC 10 Wristband incorrect/not available
- SC 11 Sample contaminated

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Incident Codes

(continued)

Note: Incident codes are based on MERS TM (US) and TESS (Canada) incident classification schemes.

Sample Handling
(Service collecting the samples)
Events that occur when a patient sample is sent for testing.
- SH 00 Detail not specified
- SH 01 Sample sent without requisition
- SH 02 Requisition and sample label don't match
- SH 03 Patient ID incomplete/illegible on requisition
- SH 04 No Patient ID on requisition
- SH 05 No phlebotomist/witness identification
- SH 06 Sample sent with incorrect requisition type
- SH 07 Patient information (other than ID) missing/incorrect on requisition
- SH 08 Requisition sent without sample
- SH 09 Data entry incorrect/incomplete/not performed
- SH 10 Sample transport issue (e.g., sample broken/inappropriate conditions)
- SH 11 Duplicate sample sent in error

Sample Receipt
(Transfusion Service)
Events that occur when a sample is received by the transfusion service.
- SR 00 Detail not specified
- SR 01 Sample accepted in error
- SR 02 Historical review incorrect/not performed
- SR 03 Demographic review/ data entry incorrect/not performed
- SR 04 Sample incorrectly accessioned

Sample Testing
(Transfusion Service)
*Events that occur during **patient sample** testing by the transfusion service.*
- ST 00 Detail not specified
- ST 01 Data entry incomplete/incorrect/not performed
- ST 02 Appropriate sample checks incomplete/incorrect/not performed
- ST 03 Computer warning overridden in error or outside SOP
- ST 05 Sample test tube incorrectly accessioned
- ST 07 Sample test tubes mixed up
- ST 09 Sample test tube mislabeled (wrong patient identifiers)
- ST 10 Equipment problem/failure/not properly QC'd
- ST 12 Sample testing not performed
- ST 13 Incorrect sample testing method chosen
- ST 14 Sample testing performed incorrectly
- ST 15 Sample test result misinterpreted

Sample Testing (continued)
- ST 16 Reagents used were incorrect/inappropriate/expired/not properly QC'd
- ST 17 ABO/Rh error caught on final check
- ST 18 Current/historical ABO/Rh mismatch
- ST 19 Additional testing not performed
- ST 20 Confirmatory check incorrect/not performed (at time work performed)
- ST 21 Administrative check incorrect/not performed (record review/audit)
- ST 22 Sample storage incorrect/inappropriate

Product Manipulation/Processing/Testing
(Transfusion Service)
Events that occur while testing, manipulating (e.g., pooling, washing, aliquoting, irradiating), processing, or labeling blood products.
- UM 00 Detail not specified
- UM 01 Data entry incomplete/incorrect/not performed
- UM 02 Record review incomplete/incorrect/not performed
- UM 03 Incorrect product (type) selected
- UM 04 Incorrect product (patient) selected
- UM 05 Product labeled incorrectly (new/updated)
- UM 06 Computer warning overridden in error or outside SOP
- UM 07 Special processing needs not checked
- UM 08 Special processing needs misunderstood or misinterpreted
- UM 09 Special processing needs performed incorrectly
- UM 10 Special processing needs not performed
- UM 11 Equipment problem/failure/not properly QC'd
- UM 12 Reagents used were incorrect/inappropriate/expired/not properly QC'd
- UM 13 Confirmatory check incorrect/not performed (at time work performed)
- UM 14 Administrative check incorrect/not performed (record review/audit)

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Incident Codes

(continued)

Note: Incident codes are based on MERS TM (US) and TESS (Canada) incident classification schemes.

Request for Pick-up
(Clinical Service)
Events that occur when the clinical service requests pick-up of a blood product from the transfusion service.

- RP 00 Detail not specified
- RP 01 Request for pick-up on wrong patient
- RP 02 Incorrect product requested for pick-up
- RP 03 Product requested prior to obtaining consent
- RP 04 Product requested for pick-up, but patient not available
- RP 05 Product requested for pick-up, but IV not ready
- RP 06 Request for pick-up incomplete (e.g., patient ID/product type missing)
- RP 07 Pick-up slip did not match patient information on product

Product Issue
(Transfusion Service)
Events that occur when the transfusion service issues blood product to the clinical service.

- UI 00 Detail not specified
- UI 01 Data entry incomplete/incorrect/not performed
- UI 02 Record review incomplete/incorrect/not performed
- UI 03 Product issued for wrong patient
- UI 04 Product issued out of order
- UI 05 Product issue delayed
- UI 06 LIS warning overridden in error or outside SOP
- UI 07 Computer issue not completed
- UI 08 Issued visibly defective product (e.g., clots/aggregates/particulate matter)
- UI 09 Not/incorrect checking of unit and/or patient information
- UI 10 Product transport issues (e.g., delayed) by transfusion service
- UI 11 Unit delivered to incorrect location by transfusion service
- UI 12 Product transport issue (from transfusion service to clinical area)
- UI 18 Wrong product issued for intended patient (e.g., incompatible)
- UI 19 Inappropriate product issued for patient (e.g., not irradiated, CMV+)
- UI 20 Confirmatory check incorrect/not performed (at time work performed)
- UI 21 Administrative check incorrect/not performed (record review/audit)
- UI 22 Issue approval not obtained/documented
- UI 23 Receipt verification not performed (pneumatic tube issue)

Satellite Storage
(Clinical Service)
Events that occur while product is stored and handled by the clinical service.

- CS 00 Detail not specified
- CS 01 Incorrect storage conditions of product in clinical area
- CS 02 Incorrect storage location in the clinical area
- CS 03 Labeling issue (by clinical staff)
- CS 04 Floor/clinic did not check for existing products in their area
- CS 05 Product transport issues (to or between clinical areas)
- CS 06 Monitoring of satellite storage incorrect/incomplete/not performed
- CS 07 Storage tracking/documentation incorrect/incomplete/not performed

Product Administration
(Clinical Service)
Events that occur during the administration of blood products.

- UT 00 Detail not specified
- UT 01 Administered intended product to wrong patient
- UT 02 Administered wrong product to intended patient
- UT 03 Transfusion not performed in error
- UT 05 Bedside check (patient ID confirmation) incomplete/not performed
- UT 06 Transfused product with unapproved IV fluid
- UT 07 Transfusion delayed beyond pre-approved timeframe
- UT 09 Transfused unsuitable product (e.g., outdated/inappropriately stored)
- UT 10 Administered components in wrong order
- UT 11 Appropriate monitoring of patient not performed
- UT 14 Transfusion volume too low (per order or SOP)
- UT 15 Transfusion volume too high (per order or SOP)
- UT 16 Transfusion rate too slow (per order or SOP)
- UT 17 Transfusion rate too fast (per order or SOP)
- UT 18 Inappropriate preparation of product
- UT 19 Transfusion protocol not followed (not otherwise specified)
- UT 22 Order/consent check incorrect/not performed
- UT 23 Transfusion documentation incorrect/incomplete/not performed
- UT 24 Transfusion documentation not returned to transfusion service
- UT 26 Transfusion reaction protocol not followed

Other

- MS 99 Other

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Occupation Codes

Laboratory		Additional Occupation Types	
IVT	IVT Team Staff	ATT	Attendant/Orderly
MLT	Medical Laboratory Technician	CSS	Central Supply
MTE	Medical Technologist	CSW	Counselor/Social Worker
PHL	Phlebotomist/IV Team	DIT	Dietician
Nursing		DNA	Dental Assistant/Technician
LPN	Licensed Practical Nurse	DNH	Dental Hygienist
CNA	Nurse Anesthetist	DNO	Other Dental Worker
CNM	Certified Nurse Midwife	DNT	Dentist
NUA	Nursing Assistant	DST	Dental Student
NUP	Nurse Practitioner	FOS	Food Service
RNU	Registered Nurse	HSK	Housekeeper
Physician		ICP	Infection Control Professional
FEL	Fellow	LAU	Laundry Staff
MST	Medical Student	MNT	Maintenance/Engineering
PHY	Attending/Staff Physician	MOR	Morgue Technician
RES	Intern/Resident	OAS	Other Ancillary Staff
Technicians		OFR	Other First Responder
EMT	EMT/Paramedic	OH	Occupational Health Professional
HEM	Hemodialysis Technician	OMS	Other Medical Staff
ORS	OR/Surgery Technician	OTH	Other
PCT	Patient Care Technician	OTT	Other Technician/Therapist
Other Personnel		PAS	Physician Assistant
CLA	Clerical/Administrative	PHA	Pharmacist
TRA	Transport/Messenger/Porter	PHW	Public Health Worker
		PLT	Physical Therapist
		PSY	Psychiatric Technician
		RCH	Researcher
		RDT	Radiologic Technologist
		RTT	Respiratory Therapist/Technician
		STU	Other Student
		VOL	Volunteer

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Incident Glossary

Incident Result

Product transfused; reaction (No recovery; harm):
A product related to this incident was transfused; the patient experienced an adverse reaction.

Product transfused; no reaction (No recovery; no harm):
A product related to this incident was transfused; the patient did not experience an adverse reaction.

No product transfused; unplanned recovery (Near miss; unplanned recovery):
No product related to this incident was transfused; the incident was discovered ad hoc, by accident, by human lucky catch, etc.

No product transfused; planned recovery (Near miss; planned recovery):
No product related to this incident was transfused; the incident was discovered through a standardized process or barrier designed to prevent errors.

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Section 5. Hemovigilance Module Denominators

Required Reporting
Facilities must report the total number of units and aliquots of specified blood components transfused and total number of discards each month. When reporting aliquots, the units from which they are made should **NOT** be counted as a transfused unit. The components transfused count should include autologous units. The total number of patient samples collected and total crossmatch procedures must also be reported. This form must be completed each month that surveillance is conducted and data can only be entered once the calendar month is over. For instance, February data must be entered after March 1st. Additionally, data cannot be entered for upcoming months.

Pathogen Reduced Blood Products
The total number of transfused units of blood components which are produced with pathogen-reduction technology (PRT) should be reported each month, if applicable. These PRT units are reported in Table 2 and are a subset of total number of units and aliquots transfused that are reported in Table 1. Table 3 relates to pathogen reduced apheresis platelets, if reported in table 2. For more guidance please refer to the Denominator QuickLearn on the NHSN Blood Safety Surveillance website.

Electronic Reporting
In January 2017, the NHSN Hemovigilance Module can accept electronically reported denominator data via clinical documentation architecture (CDA). Compared to manual reporting, electronic reporting will decrease the time required for data collection and reporting, reduce data entry errors, and increase data granularity. In order to electronically report data, facilities' software system must have CDA functionality. For more information about electronic reporting and CDA, review CDA Frequently Asked Questions on the NHSN Blood Safety Surveillance website.

Form
CDC 57.303 Hemovigilance Module Monthly Reporting Denominators

Form Instructions
CDC 57.303 Hemovigilance Module Monthly Reporting Denominators Tables of Instructions

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14.2 APPENDIX 2: Respiratory Reactions Supplementary Forms

AABB Center for Patient Safety: Respiratory Reactions Supplementary Form

Organization ID: _____ NHSN Adverse Reaction: #_____ Date of reaction: _____

Patient Details	
Diagnosis requiring transfusion of suspected components: _____	
Admitting diagnosis:	
Underlying condition:	
Transfusion reaction (check one):	☐ TRALI ☐ TACO ☐ TAD (transfusion-associated dyspnea)
Short patient narrative:	(Include underlying indication for transfusion, co-morbidities, details of alleged transfusion reactions including timing in relation to transfusion, clinical characteristics of reaction, treatment and response to treatment):

Components (enter number of units):		
	6 hours before onset of reaction	**Between 6 and 24 hours after onset of reaction**
Red Blood Cells		
Apheresis platelets		
Pooled platelets		
Plasma (FFP, FP24, Thawed plasma, Cryosupernatant)		
Granulocytes		
Other (specify): _____		

Timing of Onset of Symptoms (check the appropriate time of onset)			
☐	During the transfusion	☐	>6 <24 hours
☐	Within 1 hour	☐	>24 hours
☐	1-6 hours after cessation of transfusion		

Description of Transfusion Reaction – Please indicate "Yes" or "No" in each row (NA = not available or not applicable)				
	YES	**NO**	**NA**	**Provide specific data, if available**
Dyspnea:	☐	☐	☐	Peak resp. rate: _____
Hypoxemia: • SAO_2 <90% on room air • PaO_2/FiO_2 <300 • Other objective evidence	☐	☐	☐	SAO_2 and/or PaO_2 (before reaction): _____ Nadir SAO2 and/or PaO2: _____ Ratio PaO2/FiO2: _____

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AABB Center for Patient Safety: Respiratory Reactions Supplementary Form

Organization ID: _____ NHSN Adverse Reaction: #_____ Date of reaction: _____

Pre-transfusion Chest X-Ray: (evidence of pulmonary edema)	☐	☐	☐	**Check if present:** ☐ Bilateral diffuse infiltrates ☐ Cardiomegaly ☐ Pulmonary vascular congestion ☐ Cardiogenic edema ☐ Non-cardiogenic edema ☐ Other (describe) Brief pertinent description:
1st Post-transfusion: (Chest X-Ray evidence of pulmonary edema)	☐	☐	☐	**Check if new or worsened finding:** ☐ Bilateral diffuse infiltrates ☐ Cardiomegaly ☐ Pulmonary vascular congestion ☐ Cardiogenic edema ☐ Non-cardiogenic edema ☐ Other (describe) Brief pertinent description:
2nd Post-transfusion: (If applicable)	☐	☐	☐	**Check if new or worsened finding:** ☐ Bilateral diffuse infiltrates ☐ Cardiomegaly ☐ Pulmonary vascular congestion ☐ Cardiogenic edema ☐ Non-cardiogenic edema ☐ Other (describe) Brief pertinent description:
Was the 24 hour fluid balance positive before onset of transfusion reaction?	☐	☐	☐	Fluid balance (Liters + or -):_____ Weight change (Kg + or -): _____
Was volume overload suspected as a possible cause of the reaction? (Provide hemodynamic and/or BNP data if available)	☐	☐	☐	Pre-reaction-CVP: _____mmHg ☐NA Post-reaction-CVP: -_____mmHg ☐NA Pre-BNP: ____ (Normal Range_____) ☐NA Post-BNP:____ (Normal Range _____) ☐NA
Was there a history of congestive heart failure before transfusion? (provide ejection fraction before and after if available)	☐	☐	☐	Pre-reaction EF: _____% ☐NA Post-reaction EF: _____% ☐NA

Were there any risk factors for acute lung injury present before transfusion?

☐ Pneumonia	☐ Aspiration	☐ Severe sepsis
☐ Shock	☐ Acute pancreatitis	☐ Multiple trauma
☐ Burn injury	☐ Cardiopulmonary bypass	☐ Drug overdose
☐ Lung contusion	☐ Near drowning	☐ Toxic inhalation
☐ Other underlying pulmonary disease		

Time to Recovery

☐	>24 hours of onset of symptoms	☐	>28 days of onset of symptoms
☐	>1 <7 days of onset of symptoms	☐	No recovery (death)
☐	>7 <28 days of onset of symptoms		

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14.3 APPENDIX 3: Supplementary Questionnaire Transfusion-Transmitted Bacterial Infection

Organization ID: _____
NHSN Adverse Reaction: #_____ Date of reaction: _____

Supplementary Questionnaire
Transfusion-Transmitted Bacterial Infection

Reasons for Investigation of Bacterial Sepsis
[Why are you investigating this as Blood Component Associated Bacterial Sepsis?]

In the left column, please check the event(s) that triggered your report of sepsis associated with transfusion. In the middle column, please provide all available sign/symptom information, whether or not it was the primary trigger for the investigation.

Event	Signs and Symptoms	Time sign/symptom noted after the start of the transfusion
☐ Temperature Change	Pre-transfusion: _____°F/°C Post-reaction max: _____°F/°C	
☐ Blood Pressure Change	Pre-transfusion: _____mmHg (systolic/diastolic) Post-reaction: BP Max: _____mmHg BP Min: _____mmHg (systolic/diastolic)	
☐ Respiration rate	Pre-transfusion: _____ Post-reaction: _____ (breaths per minute)	
☐ Shock[1]		
☐ Chills/ Rigors		
☐ CNS signs and symptoms	Describe using NHSN Instructions:	
☐ Multiple organ dysfunction syndrome (progressive dysfunction of two or more major organ systems in a critically ill patient that makes it impossible to maintain homeostasis without medical intervention)	Describe:	
☐ Other:	Describe:	

[1] NHSN definition: A drop in blood pressure accompanied by a drop in cardiac output including rapid heart rate (increase to 100 beats per minute or more), rapid breathing, cutaneous vasoconstriction, pallor, sweating, decreased or scanty urine production, agitation and/or loss of consciousness that required fluid resuscitation, with or without inotropic support (9_2013).

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Organization ID: _____
NHSN Adverse Reaction: #_____ Date of reaction: _____

Did clinicians at your hospital diagnose sepsis in this patient using SIRS criteria[2]?
☐ Yes ☐ No ☐ Don't Know

Suspected component (check all that apply):
☐ RED BLOOD CELLS ☐ PLATELETS ☐ PLASMA ☐ OTHER: _____

Laboratory Testing: Bacteria				
	Culture Performed (check one)	**Culture Results (check one)**	**Identity of Organism**	**Date/Time of Sampling**
Patient Pre-transfusion: (check all that apply)				
☐ Blood	☐ Yes ☐ No ☐ Don't Know	☐ Positive ☐ Negative ☐ Don't Know		
☐ Urine	☐ Yes ☐ No ☐ Don't Know	☐ Positive ☐ Negative ☐ Don't Know		
☐ Other: _____	☐ Yes ☐ No ☐ Don't Know	☐ Positive ☐ Negative ☐ Don't Know		
Patient Post-transfusion: ☐ Blood ☐ Other: _____	☐ Yes ☐ No ☐ Don't Know	☐ Positive ☐ Negative ☐ Don't Know		
Suspect Unit(s)[3]:	☐ Yes ☐ No ☐ Don't Know	☐ Positive ☐ Negative ☐ Don't Know		
Suspect Unit(s): Final Result from platelet QC culture done at collection facility (if known and applicable).	☐ Yes ☐ No ☐ Don't Know	☐ Positive ☐ Negative ☐ Don't Know		
Point-of-issue bacterial screening result if performed (e.g. PGD or BACTx)?	☐ BACTx ☐ PGD ☐ Other: _____	☐ Positive ☐ Negative ☐ Don't Know		

Did co-components from the involved donation cause septic reaction(s) in other recipients?	☐ Yes ☐ No ☐ Don't Know
If bacterial strain(s) were isolated from the patient and the implicated component and/or co-components, were they evaluated for identity? If yes, please check which method was used:	☐ Yes ☐ No
☐ Antimicrobial Sensitivity ☐ RFLP/PFGE ☐ Sequencing ☐ Other (please describe): _____	
If agents were evaluated for identity, were the donor and patient agents identical?	☐ Yes ☐ No ☐ N/A
Were there other documented, concurrent infections in the patient? If yes, please describe (type of infection/organism):	☐ Yes ☐ No

[2] ACP/SCCM Consensus Panel Guidelines.
Sepsis is culture-documented infection plus two or more of the following
- T of >38C or <36C
- Heart rate >90
- RR >20
- WBC count >12000 or <4000 or ≥10% band forms

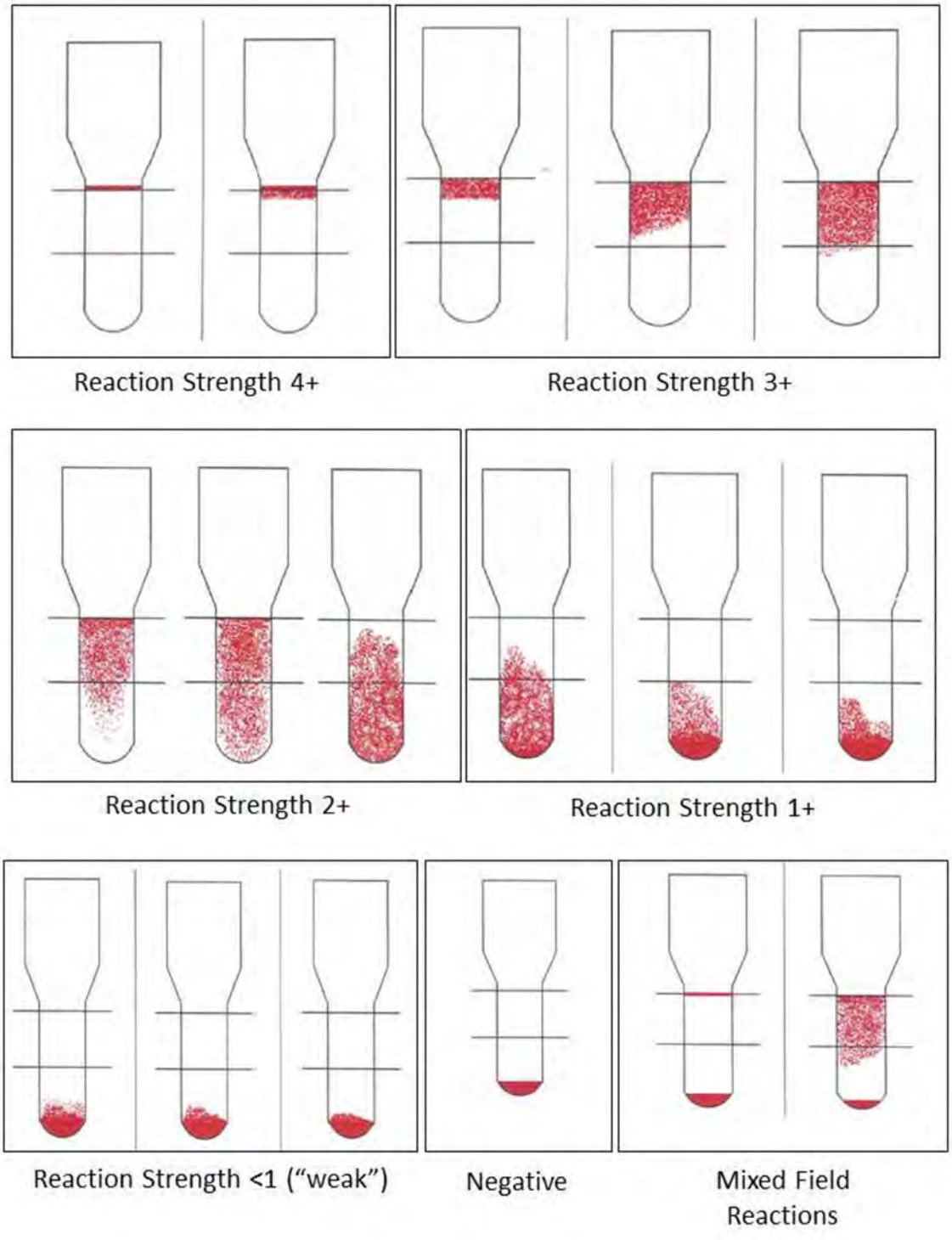
[3] Sample from implicated unit. Cultures performed only with an integral segment, unless positive, should be considered NOT performed since, due to low concentrations of bacteria, they may be sterile at the time they are sealed in the collection facility.

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14.4 APPENDIX 4: Reading and Grading Gel Card Hemagglutination Reactions



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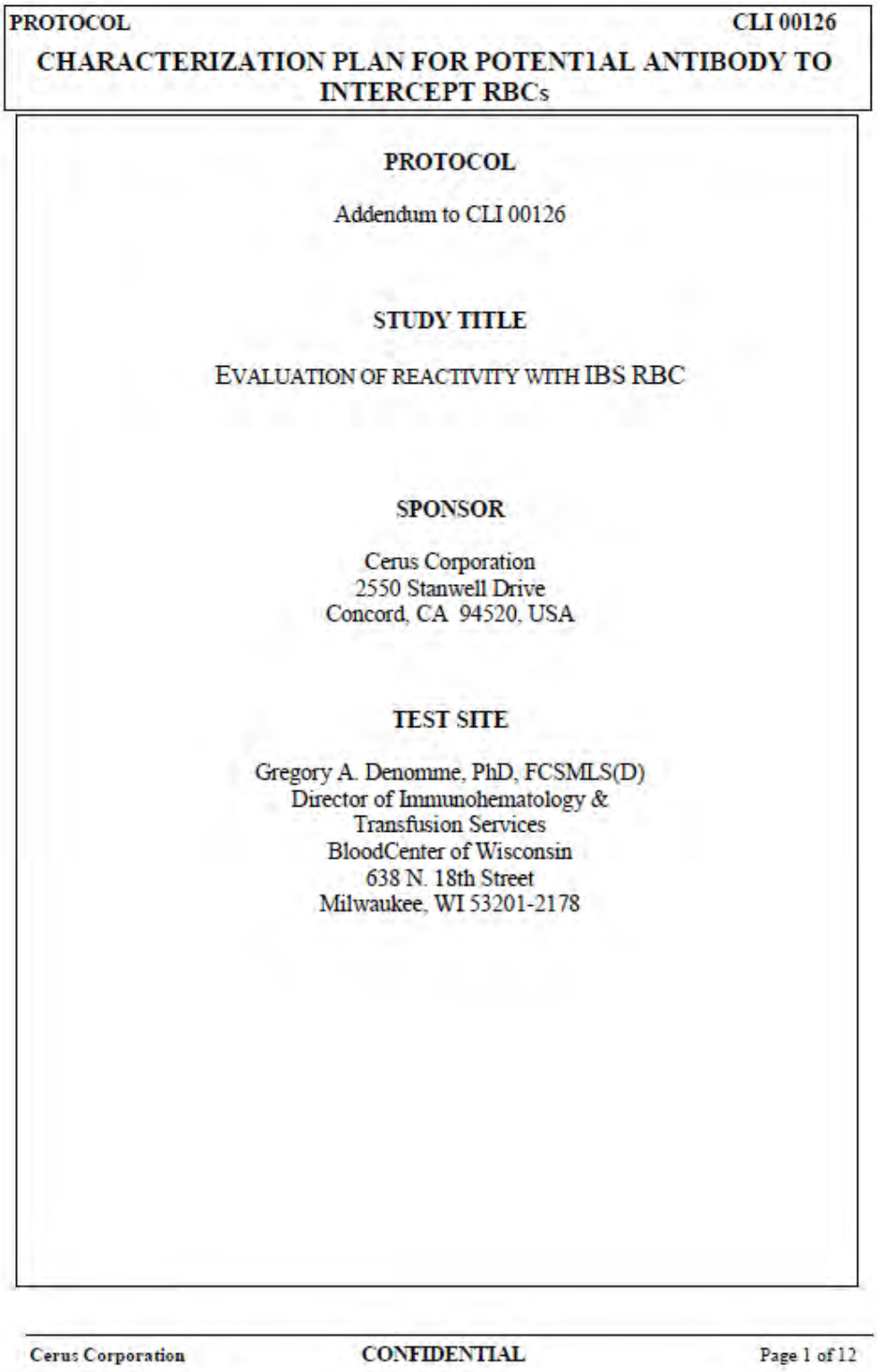
14.5 APPENDIX 5: Expanded WHO Bleeding Scale (Miller 1981 & McCullough 2004)

Organ system	Bleeding grade	
	1	2
Mucocutaneous		
Epistaxis	< 1 h in duration	> 1 h in duration
Oropharyngeal	< 1 h in duration	> 1 h in duration
Petechiae/purpura	Localized petechiae of skin or oral mucosa; purpura < 1-inch diameter	Purpura > 1-inch diameter; generalized petechiae or purpura
Gastrointestinal		
Melena	NA	Melanotic stool with positive occult blood
Rectal bleeding/ hematochezia	Occult blood in stool; no visible blood	Visible blood in stool
Hematemesis	NA	Occult or visible blood in vomit or gastric contents
Genitourinary		
Hematuria	< 1+ (slight, trace, small) blood in urine	≥ 2+ (moderate)
Vaginal bleeding, abnormal	Spotting; < 2 saturated pads/d	> 2 saturated pads/d
Bronchopulmonary	NA	Hemoptysis; blood-tinged sputum; bloody bronchopulmonary lavage
Musculoskeletal and soft tissue	NA	Spontaneous hematoma; any joint bleed
Body cavity (pleural, peritoneal, pericardial, retroperitoneal)	NA	RBCs on microscopic examination of any body fluid
Central nervous system	NA	Retinal bleeding without visual impairment
Invasive sites	NA	Any bleeding around a catheter, venipuncture site, or other invasive or surgical site

Grade 3 bleeding requires RBC transfusion; grade 3 body cavity bleeding is grossly bloody body fluid; grade 3 central nervous system (CNS) bleeding is bleeding on computed tomography or magnetic resonance imaging scan without clinical consequence. Grade 4 bleeding is associated with hemodynamic instability (hypotension; > 30 mm Hg decrease in systolic or diastolic blood pressure) or fatal bleeding; grade 4 musculoskeletal bleeding is associated with a permanent debilitating joint change; grade 4 CNS bleeding is CNS bleeding with neurologic symptoms and signs, or retinal bleeding with visual impairment (field deficit). Expanded scale is based on WHO bleeding scale from Miller et al.[29] NA indicates not applicable.

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14.6 APPENDIX 6: Evaluation of Reactivity with IBS RBC



PROTOCOL CLI 00126

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

PROTOCOL

Addendum to CLI 00126

STUDY TITLE

EVALUATION OF REACTIVITY WITH IBS RBC

SPONSOR

Cerus Corporation
2550 Stanwell Drive
Concord, CA 94520, USA

TEST SITE

Gregory A. Denomme, PhD, FCSMLS(D)
Director of Immunohematology &
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BloodCenter of Wisconsin
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PROTOCOL **CLI 00126**

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

1.0 INTRODUCTION

The INTERCEPT Blood System for RBC uses the small molecule Amustaline to form covalent crosslinks within nucleic acids of contaminating pathogens and residual leukocytes, preventing their replication. Amustaline (also referred to as S-303) is a modular compound that decomposes by hydrolysis to the non-reactive compound S-300. Glutathione (GSH), a natural antioxidant, is included in the treatment process to quench unreacted S-303.

Clinical development of the INTERCEPT System for RBC initially involved a previous formulation and processing system (First Generation Process). During two Phase 3 studies (patients with acute anemia secondary to cardiovascular surgery (RBC 3A01) and patients with chronic anemia due to thalassemia or sickle cell disease (RBC 3B01) an unexpected cross-match reactivity specific to INTERCEPT RBCs was found in 2 patients in the chronic anemia study. The antibodies were low-titer (which declined to undetectable levels over 11 months) and were specific for the acridine moiety in S-303. Neither patient had demonstrable clinical evidence of accelerated red cell destruction in association with these antibodies (Benjamin et al, 2005). Follow-up evaluation demonstrated no adverse health effects and the potential for physiologic activity of the anti-acridine antibody evaluated by a monocyte monolayer phagocytosis assay (Nance, et al. 1987; Arndt and Garratty 2004) indicated that these antibodies were unlikely to cause a hemolytic transfusion event. A Second Generation System was subsequently developed to reduce the density of INTERCEPT treatment-related membrane bound acridine adducts by increasing the concentration of the GSH quencher by 10-fold to 20 mM.

Using established routine methods, this document outlines the procedure for characterization of to any treatment-emergent antibody with confirmed specificity to IBS RBCs associated with clinically significant hemolysis.

At study entry and at specific times during the study, subject plasma/serum samples are tested for the presence of antibody against INTERCEPT RBC. The initial testing will be performed at the site with patient plasma or serum and Cerus Frozen Reagent RBCs using a commercial gel card IAT assay.

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PROTOCOL **CLI 00126**

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

If a study site experiences reactivity/agglutination with patient plasma and INTERCEPT RBCs, an additional sample of plasma or serum will be sent to the central testing lab (BCW) for characterization.

1.1 RESPONSIBILITIES

Clinical department management or a designated alternate at the hospital blood center and the Central Testing Laboratory at Blood Center of Wisconsin are responsible for implementing this procedure and revising it whenever necessary.

All trained personnel are responsible for performing this procedure to assure that quality standards are met.

1.2 SCOPE AND OBJECTIVE

This document contains the procedure for characterization of positive reactivity with specificity (presumed or confirmed) against INTERCEPT treated RBC at any time during the study.

If a patient develops an antibody, the Investigator will collect patient samples (if possible, EDTA plasma and serum) and send them, along with the Patient Information form (FRM 00782) to the Blood Center of Wisconsin (BCW) who will act as the Central Testing Laboratory for antibody evaluation.

2.0 MATERIALS AND METHODS

Lot numbers, serial numbers, and expiration dates will be recorded for all materials identified in this protocol.

- 10 x 75 mm borosilicate glass tubes (Kimble-Chase, Vineland, NJ)
- IgG gel cards, MDP081, Ortho Diagnostics, Raritan, NJ
- ID-Diluent 2, Ortho Diagnostics, Catalog number MTS9230
- Isotonic (0.85%) NaCl, EK Industries, Joliet, IL Product code 12441
- 9% w/v NaCl in H_2O
- 2.5% w/v NaCl in H_20, lot numbers referenced in each appropriate section
- MLB2 Modified LISS, BioRad, Hercules, CA Reference number 8236100

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- Human Serum Albumin (HSA), Millipore, Kankakee, Illinois
- Frozen Reagent RBC panels (Primary and Secondary panels)
- Monoclonal anti-acridine antibody positive control (2S-197-2M1, Antibody Solutions, Sunnyvale, CA. SPC-COA 00035)
- 2-mercapto ethanol (Sigma Aldrich, M6250)

For specificity determinations

- Cerus acridine compound S-300 (Lot number of compound will be recorded with the procedure)
- GSH (Identity/Code P/N 271) (Cerus SPC 00271)

Equipment

- Ortho gel card incubator (Ortho Clinical; MTS9680) or equivalent
- Ortho Gel card centrifuge (Ortho Clinical; MTS5160) or equivalent

3.0 REAGENT RBC PANELS

Reagent RBC panels have been prepared under contract from Cerus corp. from RBC components collected from different blood group O donors with defined red cell antigenic composition representative of the types of RBC antigens associated with clinically relevant immunologic reactions.

For the Primary "antibody detection" or "screening" panel, RBCs from 3 different donors were used and together, these 3 donor RBC components provided a reagent cell panel with a combination of intrinsic RBC antigens able to detect most clinically significant antibodies.

In addition to the "Primary 3 cell screening panel", a 6 donor RBC cell "Secondary identification panel" has been produced to aid identification of antibody should results from the Primary panel be equivocal or indeterminate. As with the Primary panel, each RBC has untreated or labeled with either high or low levels of acridine. For the Secondary "antibody identification" panel, an additional 6 different donors were used, each again with specific antigen

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phenotypes to allow characterization of any positive response from the primary panel.

Thawing and use of Reagent frozen RBC is detailed in Cerus document INS 00593.

4.0 MOUSE MONOCLONAL ANTI-ACRIDINE ANTIBODY (POSITIVE CONTROL)

For each antibody analysis, a monoclonal anti-acridine antibody will be used as a positive control to demonstrate the detection of acridine on the surface of the frozen S-303 RBC panel cells. The monoclonal antibody was produced from a hybridoma obtained from a mouse immunized with KLH-conjugated S-197, a stable non-hydrolysable acridine analog of amustaline and specificity and sensitivity for acridine on the red cell surface has been extensively characterized (SUD 00734) The monoclonal antibody reacts with High and Low S303 treated RBC and fails to react with RBCs that had not been treated with INTERCEPT.

5.0 PATIENT INFORMATION FORM

This information must be sent with the patient samples to the Central Testing Laboratory and include the following information:

- Patient identifier (patient ID number)
- Patient date of birth
- Patient Blood Group, including ABO and D (if available)
- Type of anticoagulant used and date of blood collection into anticoagulant
- IAT and DAT testing result
- Presence and identity of preexisting or newly acquired alloantibody against intrinsic red cell antigens
- Copies of laboratory worksheets of the tests performed identifying allo- or S-303 antibodies

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- Any additional comments which may be useful to the Central Laboratory can be added to the last section of the form

6.0 SAMPLES FOR ANALYSIS

Plasma or serum samples for antibody characterization will be prepared per Cerus INS 00733. The samples will be frozen and shipped to BCW (FRM 00781).

Gregory A. Denomme, PhD, FCSMLS (D)
Director of Immunohematology & Transfusion Services
Blood Center of Wisconsin
638 N. 18th Street, Milwaukee, WI 53201-2178

Notify the Central testing laboratory (BCW) that there is a World Courier delivery on the way by sending a copy of the Shipping Invoice by email or by FAX.

7.0 SAMPLE ANAYSIS AT BCW

On arrival at BCW the plasma/serum sample will undergo extensive characterization to include confirmation of reactivity identified at the clinical site, characterization of antibody specificity, antibody titer, antibody type and subtype, and thermal amplitude. Allo-adsorption may be performed in cases with potential autoantibody and complement activation studies may be performed to characterize the hemolytic potential of IgM antibodies

All of the tests performed at BCW will be performed according to local SOPs on file at the blood center.

7.1 CONFIRMATION OF INTERCEPT RBC REACTIVITY WITH FROZEN RBC PANEL CELLS

The gel column agglutination technique developed and validated for use with human serum to detect antibodies to INTERCEPT RBC will be used in this characterization (VAL 00257).

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As per manufacturer's recommendation, 50 µL of Cerus Reagent RBC Primary panel cells at 0.8% hematocrit in ID-Diluent 2 (INS 00593) will be added to a column in the gel card followed by 25 µL of patient plasma or serum and gel cards incubated at 37°C for 15 minutes in the gel card incubator (Ortho Clinical MTS 9680). After incubation, the gel cards are centrifuged with a speed of ~1000 rpm for 10 minutes (Ortho Clinical MTS 9650), the hemagglutination score will be noted as an indication of antibody bound to the RBCs (INS 00625).
Using (i) High acridine, (ii) Low acridine, and (iii) untreated RBCs in a 3-cell screening procedure, reactivity to the INTERCEPT treated RBCs with no reactivity with corresponding untreated control cells is an indication that antibodies specific to S-303 RBC are present.

Reactivity will also be confirmed by traditional LISS tube agglutination with and without AHG.

7.2 ANTIBODY CHARACTERIZATION

7.2.1 ANTIBODY TITER

Serial doubling dilutions of patient sample will be made using 6% albumin in saline as diluent to determine the positive reaction limit of the gel column agglutination assay using untreated RBCs, or RBCs carrying both High and Low acridine adducts. The titer will be recorded as the inverse of the highest dilution that gave an observable, reproducible positive agglutination result with INTERCEPT treated RBCs. The accepted variation in strength of agglutination, particularly with weak reactivity, is +/- 1 doubling dilution (VAL 00257).

In conjunction, a series of doubling dilution will also be made of the murine monoclonal anti-S197 antibody as positive control using 6% albumin in saline as diluent.

7.2.2 ANTIBODY SPECIFICITY BY HEMAGGLUTINATION INHIBITION

To establish specificity of patient sample reactivity, an acridine competition assay using agglutination inhibition (neutralization) with S-300 in solution

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(S-300 is the major acridine degradation product of INTERCEPT treated RBC) will be used (INS 00732).

Patient plasma/serum (25 µL) will be incubated with increasing concentrations of S-300 in 1.5 mL microcentrifuge tubes (5 µL per tube) and incubated for 15 minutes at 37°C. During this time, 50 µL of 0.8% INTERCEPT RBC (INS 00593) with high levels of acridine will be added to the upper well of the gel column. At the end of the incubation time (during which anybody in patient sample will bind to the free acridine), 25 µL of the incubated plasma/S-300 mixture will be added to the INTERCEPT RBC in the gel card and incubated and centrifuged according to standard practice.

If the agglutination is reduced in an acridine dose-dependent manner this indicates that the antibody in the sample had specificity for acridine (S-300). As a positive neutralization control in each determination of specificity, incubation of S-300 compound with the monoclonal anti-S197 antibody will be included.

7.2.3 IMMUNOGLOBULIN ISOTYPE

Gel column agglutination will be performed with monoclonal anti-IgG_1 & IgG_3 reagent in the gel cards. Reactivity in this card indicates the presence of an IgG_1, IgG_3 or an IgM antibody. Absence of reactivity in samples that have previous reacted in anti IgG Gel cards, suggests the presence of an IgG2 or IgG4 subtype antibody. In order to exclude an IgM antibody, the procedure is performed with 'blank' or buffer only gel cards. Hemagglutination in a blank card (no anti-IgG, IgG1 or IgG3 reagent) is an indication that an IgM isotype antibody is present.

If an IgM antibody is suggested by the agglutination pattern in the buffer card, plasma will be treated with 2-Mercaptoenthanol (2-ME) to destroy the J-chain of IgM molecules. 2-ME treatment essentially destroys the ability of IgM to cause direct hemagglutination and will be used to further confirm the presence of IgM anti-S-303 in standard clinical tube test method. Both IgG_1 and IgG_3 isotype subclasses have the potential to activate complement and antibody dependent cellular toxicity and therefore the potential for causing hemolysis and/or extravascular clearance in vivo.

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7.2.4 THERMAL AMPLITUDE TEST

An anti-S-303 antibody will be evaluated at different temperatures to determine the temperature range of reactivity. Standard tube tests will be performed at Room Temperature (RT) and at (or near) 37°C to determine the temperature range of reactivity. Antibodies that react at RT only are considered clinically insignificant. Antibodies that react at or near 37°C indicate the potential for binding at body temperature. Binding of antibodies at body temperature in vivo can result in their intra- or extravascular destruction, i.e. the potential for hemolysis.

7.2.5 COMPLEMENT ACTIVATION

Some IgG antibodies may activate complement due to the initial binding to the RBCs, which can lead to hemolysis if this occurs in vivo. Tube tests can be performed to combine RBCs and serum at 37°C to determine if anti-S-303 antibodies can activate complement. These assays rely on an anti-globulin reagent that contains anti-C3b antibodies.

7.2.6 COMPLEMENT-MEDIATED IN VITRO HEMOLYSIS.

A bioassay can assess the direct potential for anti-S-303 to activate complement that proceeds to completion with an endpoint of hemolysis (Cunnion et al., 2016). In brief, serum or plasma are added in a calcium/magnesium buffer that facilitates complement activation through to C9 (complete hemolysis). The combined RBCs and serum are incubated at 37°C. Hemolysis is measured by optical density reading at 412nm. This in vitro hemolysis assay is a direct measure of the potential for hemolysis in vivo.

8.0 DEVIATIONS

Any deviations to the protocol or standard operating procedures during the performance of this study will be documented and included in the final report.

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9.0 DOCUMENTATION AND REPORT

Each run will be documented. Sampling and sample preparation will be recorded on data capture sheets. Upon completion of this protocol, a report for this study will be prepared.

10.0 DATA RETENTION

All raw data will be retained by BCW and copies will be provided to Cerus and retained in the Cerus Corporation archives, managed from 2550 Stanwell Drive, Concord, CA 94520.

11.0 COMPLIANCE

Unless otherwise stated, all procedures will be performed according to Cerus or BCW operating procedures.

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APPENDIX 1 REFERENCES

- Benjamin et al, 2005, "Therapeutic efficacy and safety of red blood cells treated with a chemical process (S-303) for pathogen inactivation: a Phase III clinical trial in cardiac surgery patients." Transfusion. 2005 Nov;45(11):1739-49.
- Nance, et al. 1987 "Predicting the clinical significance of red cell alloantibodies using a monocyte monolayer assay". TRANSFUSION 1987;27:449-452.
- Arndt and Garratty 2004, A retrospective analysis of the value of monocyte monolayerassay results for predicting the clinical significance of blood group alloantibodies. Transfusion Volume 44, September 2004Cunnion et al, Transfusion 2016;56:1845-8.

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PROTOCOL **CLI 00126**

CHARACTERIZATION PLAN FOR POTENTIAL ANTIBODY TO INTERCEPT RBCs

APPENDIX 2 CERUS REFS

CLI 00033; RBC3A01

FRM 00782; "CLI 00126, PATIENT INORMATION TO ACCOMPANY SAMPLES FOR ANTIBODY INVESTIGATION AT CENTRAL TESTING LABORATORY

INS 00593; FREEZİNG AND THAWİNG OF RED BLOOD CELL SAMPLES

INS 00625; READİNG AND GRADİNG GEL CARD HEMAGGLTUİNATİON REACTİON WİTH CERUS FROZEN RED CELL PANELS

INS 00732 " AGGLUTINATION INHIBITION TO DETERMINE SPECIFICITY OF A POSITIVE REACTIVITY TO INTERCEPT TREATED RBCS IN CLI 00126"

INS 00733; PREPARATION OF SAMPLES FOR ANTIBODY CHARACTERIZATION AT A REFERENCE LABORATORY, CLI 00126"

FRM 00781 for "SHIPPING INVOICE FOR ANTIBODY TESTING SAMPLES FOR CLI 00126"

SPC-COA 00035; MOUSE MONOCLONAL ANTİBODY AGAİNST THE S-303 ANALOG, S-197 (2S197-2M1)

SUD 00734; INHİBİTİON OF AGGLUTİNATİON WİTH S-300 TO DETERMİNE ACRİDİNE SPECİFİCİTY OF A POSİTİVE REACTİON TO INTERCEPT TREATED RBCS

VAL 00257; A VALIDATION STUDY FOR THE USE OF GEL COLUMN AGGLUTINATION TECHNOLOGY IN THE DETECTION OF IGG AND IGM SERUM AND PLASMA ANTIBODY TO S-303-TREATED RBCS

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