A Phase I, Multi-Center, Open-Label, Dose Escalation Study of Thrombosomes® in Bleeding Thrombocytopenic Patients in Three Cohorts

Cellphire, Inc.
Clinical Protocol # 2017-1 Version 2.0

October 18, 2018

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Emily Rossiter		Regulatory	
Joan Pehta, MD		Medical Consultant	

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1.1 Principal Investigator

Roles and Responsibilities of PI: Eligibility review, evaluate adverse events, adhere to GCP, and supervise staff participation in study.

PI Name	Institution	Contact Details
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1.2 Study Location and Testing or Other Medical/Technical Departments/Institutions Involved in Study

Institution Name	Institution Address	Procedure or Test
University of Cincinnati Medical Center	Hematology/Oncology, 234 Goodman Street, Cincinnati, OH, 45219	Patient Infusion and post-infusion 24 hour observation and monitoring
University of Cincinnati Medical Center Clinical Laboratory	234 Goodman Street, Cincinnati, OH, 45219	All laboratory testing except those tests performed by Haemtech Biopharma Services
Haemtech Biopharma Services	57 River Road, Essex Junction, VT, 05452	TAT, PF 1+2, TGA
City of Hope National Medical Center	1500 E. Duarte Road, Duarte, CA 91010	Patient Infusion and post-infusion 24 hour observation and monitoring
City of Hope National Medical Center, Division of Pathology	1500 E. Duarte Road, Duarte, CA 91010	All laboratory testing except those tests performed by Haemtech Biopharma Services
Dartmouth-Hitchcock Medical Center	1 Medical Center Drive, Lebanon, NH 03756	Patient Infusion and post-infusion 24 hour observation and monitoring
Dartmouth-Hitchcock Medical Center Dept of Pathology and Laboratory Medicine Clinical Laboratory	1 Medical Center Drive, Lebanon, NH 03756	All laboratory testing except those tests performed by Haemtech Biopharma Services
University of Michigan	1500 E. Medical Center Drive, Ann Arbor, MI 48109	Patient Infusion and post-infusion 24 hour observation and monitoring
University of Michigan Hospitals- Department of Pathology	1500 E. Medical Center Drive, Ann Arbor, MI 48109	All laboratory testing except those tests performed by Haemtech Biopharma Services
The University of Texas/ MD Anderson Cancer Center	1515 Holcombe Blvd., Houston, TX 77030	Patient Infusion and post-infusion 24 hour observation and monitoring
The University of Texas/ MD Anderson Cancer Center, Division of Laboratory Medicine	1515 Holcombe Blvd., Unit 024, Houston, TX 77030	All laboratory testing except those tests performed by Haemtech Biopharma Services
Georgetown University Medical Center	3800 Reservoir Road, NW Washington, DC 20007	Patient Infusion and post-infusion 24 hour observation and monitoring

Dept. of Lab MedStar Georgetown University Hospital	3800 Reservoir Road, NW, 1 Main Rm M1341Washington, DC 20007	All laboratory testing except those tests performed by Haemtech Biopharma Services
Haukeland University Hospital Dept. of Hematology/Immunology and Transfusion Medicine	Postboks 1400, Bergen Norway 5021	Patient Infusion and post-infusion 24 hour observation and monitoring
Haukeland University Hospital Dept. of Immunology and Transfusion Medicine Dept. of Medical Biochemistry and Pharmacology	Postboks 1400, Bergen Norway 5021	All laboratory testing except those tests performed by Haemtech Biopharma Services

1.3 Program Phase

The following protocol governs a Phase 1 dose escalation clinical trial.

1.4 Time Required for Study Completion

First Patient Treated: Q1 2018

Last Patient Last Visit: Q2 2019

1.5 List of Acronyms

ADR	Adverse Drug Reaction
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BARDA	Biomedical Advanced Research and Development Authority
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAT	Calibrated Automated Thrombogram
CBC	Complete Blood Count
CBER	Center for Biologics Evaluation and Research
CCI	Corrected Count Increment
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CNS	Central Nervous System
COR	Contracting Officer's Representative (BARDA)
COX	Cyclooxygenase
CPTP	Clinical Pretest Probability
CRC	Clinical Research Center
CRO	Clinical Research Organization
CRF	Case Report Form
CSTD	Closed System Transfer Device
CTPA	Computed Tomography Pulmonary Angiogram
DIC	Disseminated Intravascular Coagulation
DMC	Data Monitoring Committee
DOT	Department of Transportation

DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDP	Fibrin Degradation Products
GVHD	Graft-versus-Host Disease
IND	Investigational New Drug
IUD	Intra-Uterine Device
EKG	Electrocardiogram
GGT	Gamma Glutamyl Transferase
HIPAA	Health Insurance Portability and Accountability Act
hs	High sensitivity
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICSI	Institute for Clinical Systems Improvement
INR	International Normalized Ratio
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
LDH	Lactate Dehydrogenase
MI	Myocardial Infarction
NCI	National Cancer Institute
NHSN	National Healthcare Safety Network
NIH	National Institutes of Health
NZWR	New Zealand White Rabbit
OHRP	Office for Human Research Protections
PE	Pulmonary Embolism
PEF	Peak Expiratory Flow
PERC	Pulmonary Embolism Rule-out Criteria
PF	Prothrombin Fragment
PI	Principal Investigator
Plt	Platelet
PT	Prothrombin Time
RBC	Red Blood Cell
RR	Respiration Rate
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event

SOP	Standard Operating Procedure
TAT	Thrombin Antithrombin
TEAE	Treatment Emergent Adverse Event
TEG	Thromboelastography
TGA	Thrombin Generation Assay
TIA	Transient Ischemic Attack
TGPU	Thrombin Generation Potency Units
USP	United States Pharmacopeia
VTE	Venous Thromboembolism
WFI	Water for Injection
WHO	World Health Organization

1.6 Background

Traumatic injury and massive uncontrollable hemorrhage are major public health problems in the United States[1]. Despite rapid, significant, advances in medicine and technology, hemorrhage treatment has in many ways lagged behind other blood product therapies such as coagulation factors and plasma proteins. A systemic hemostatic agent has the potential to fill unmet medical needs in non-compressible bleeding such as internal hemorrhage or diffuse vascular bleeding. Thrombosomes® treatment, if proven safe and effective in human trials, could assist in the management of blood loss associated with trauma, uncontrolled internal bleeding, and/or non- compressible hemorrhage.

In July of 2016, Cellphire completed a clinical study under an exploratory IND in 15 subjects (Thrombosomes n=10 and Control n=5) who received ascending doses of either: 1) Thrombosomes ranging from 1/1,000 to 1/10 of the projected minimum effective dosage (~1.89 x 10^8 Thrombosomes particles per kg or 330 Thrombin Generation Potency Units (TGPU) per kg), or 2) Thrombosomes Control (the mixture of excipients used to stabilize Thrombosomes but without the platelet component). The highest dose achieved was 1.55 x 10^7 particles per kg which has the potential to produce 27 IU of thrombin in-vitro.

There were no serious adverse events (SAEs) including deaths or stopping rules met on study, no decrease of platelet count of 20% or more from baseline, and no clinically significant changes in platelet count (change of 5% from baseline combined with post-baseline result outside of normal ranges) that occurred during the study. No statistically significant differences were seen when comparing the changes in platelet count between baseline and post-infusion values for subjects in Thrombosomes and Control groups.

Although this study, and more specifically the individual treatment cohorts, contained a small number of subjects, which led to high variability in reported AEs, the frequency and nature of TEAEs reported in this study are consistent with AEs that are typically observed in a healthy volunteer population. Overall, no clinically significant abnormities were reported after infusion of Thrombosomes, and the results were similar between the control and treated cohorts.

1.7 Product Information & Indications for Use

Thrombosomes are a lyophilized product prepared from a pool of group O human platelets (collected from 5-10 donors) that are being developed for the treatment of uncontrolled hemorrhage. Each vial from each lot of Thrombosomes contains a mean of 1.7 x 10^9 Thrombosomes particles per ml and an associated activity of approximately 3400 TGPU per ml after rehydration with 10 ml of sterile water for injection. Based upon efficacy studies in a thrombocytopenic New Zealand White Rabbit (NZWR) ear bleed model, the lowest observed efficacious dose was (1.89 x 10^8 particles per kg or 330 TGPU per kg). Refer to the *Investigator's Brochure* for additional information.

[1] National Highway Traffic Safety Administration Fatality Analysis Reporting System (FARS) 1975-2009 – http://nhtsa.gov/FARS

1.8 Objectives

The primary and secondary objectives of this trial, conducted in thrombocytopenic patients (platelet count ≥ 5,000/ μL and ≤ 70,000/μL) with modified World Health Organization (WHO) Grade 1* or 2 bleeding are:

1.8.1 Primary

- Assess the safety of infusing increasing doses (approximately 5 ml, 10 ml, and 20 ml) of allogeneic Thrombosomes which are equivalent to approximately 9.45 x 10^7 particles/kg or 165 TGPU per kg, 1.89 x 10^8 particles/kg or 330 TGPU per kg and 3.78 x 10^8 particles/kg or 660 TGPU per kg, respectively.

1.8.2 Secondary

- Assess the effect, on WHO bleeding score, of increasing doses of allogeneic Thrombosomes.
- Assess the effect of increasing doses of allogeneic Thrombosomes on measures of coagulation.

* Note: Only a subset of patients with Grade 1 bleeding who have either epistaxis, hematuria, oral petechiae, oropharyngeal bleeding, or bleeding at invasive or other wound sites.

1.9 Study Design

1.9.1 Introduction

This study will require enrollment of patients into three cohorts in order to evaluate, in a dose-escalation manner, the safety, and preliminary impact on bleeding, and the preliminary effect on coagulation measures of increasing doses of allogeneic Thrombosomes. Data from this study will provide information on the safety, and possibly potency of three increasing doses of Thrombosomes in order to support the design of future clinical protocols in bleeding patients. The proposed starting dose in this protocol is approximately five (5) times the highest dose used in a previous dose escalation study in normal healthy volunteers. For further information regarding minimum effective dose, maximum feasible dose and safety margins from previous clinical and non-clinical investigations, see the Investigator's Brochure.

1.9.2 Methodology

This is a Phase 1, multicenter, open-label, dose-escalation study in hospitalized, bleeding, and thrombocytopenic patients. Patients with modified WHO Grade 1 (see note following Table 1. Cohort Assignment) or Grade 2 bleeding due to hematology/oncology diseases or bone marrow aplasia secondary to cancer chemo/radiotherapy will be enrolled on study and treated with allogeneic Thrombosomes (See

Appendix A- Modified WHO Bleeding Score). Patients with WHO Grade 0, 3, or 4 bleeding do not meet eligibility criteria for enrollment. The protocol will require three cohorts of patients consisting of 8 patients in each cohort for a total of 24 patients (See Table 1. Cohort Assignment).

Table 1. Cohort Assignment				
Cohort	1	2	3	Total
	n	**n**	**n**	**n**
WHO Grade 1*or 2	8	8	8	24

Note: *Only a subset of patients with Grade 1 bleeding who have either epistaxis, hematuria, oral petechiae, oropharyngeal bleeding, or bleeding at invasive or other wound sites.

1.9.2.1 All Cohorts

Informed consent will be obtained from thrombocytopenic (platelet count ≥ 5,000/ μL and ≤ 70,000 per μl) patients who are actively bleeding or are at risk of active bleeding within the 4 weeks of initial screening. Patients are eligible who have had a documented bleeding episode(s) within the previous 4 days of screening. If they pass screening, they will be enrolled and infused. Patients who are not actively bleeding, but who are at risk for active bleeding based on medical history and prognosis (projected clinical course) within 4 weeks from their initial screening, will be monitored for active bleeding. If the patient was not actively bleeding at the time of screening, but bleeding occurs within 4 days (+ 6 hours) of initial screening, the patient does not need to be rescreened, but must have a WHO bleeding assessment and a CBC at baseline. If the patient was not actively bleeding at the time of screening, but bleeding occurs greater than 4 days and within 4 weeks of initial screening, the patient will be rescreened, enrolled and infused. Patients who are not infused within 4 weeks of initial screening are withdrawn from study. Patients who were withdrawn from study may be re-entered into study if they were: 1) previously not infused with Thrombosomes, and 2) meet all the enrollment requirements of study. All enrolled patients will be assigned to cohorts based on order of enrollment and timing of infusion of Thrombosomes.

All enrolled patients with active bleeding of modified WHO Grade 1 (subset of patients with either epistaxis, hematuria, oral petechiae, oropharyngeal bleeding, or bleeding at invasive or other wound sites) or Grade 2 bleeding will receive Thrombosomes. Grades 0, 3, or 4 bleeding are not inclusion criteria for enrollment. Active bleeding is defined as to occur within 4 days of infusion. If the patient progresses to grade 3 or 4 bleeding during that time, they will be excluded from the study and will not be infused. Doses will be adjusted per weight of each patient. The starting dose for patients in Cohort 1 will be approximately 5 ml of Thrombosomes or approximately 9.45×10^7 particles/kg or 165 TGPU per kg by IV infusion. The dose for patients in Cohort 2 will be approximately 10 ml of Thrombosomes or approximately 1.89×10^8 particles/kg or 330 TGPU per kg by IV infusion. The dose for patients in Cohort 3 will be one dose of approximately 20 ml of Thrombosomes or approximately 3.78×10^8 particles/kg or 660 TGPU per kg by IV infusion. See Table 2.

Pre-infusion, infusion (Day 1), and post-infusion follow up through Day 30 (+2 days) will be performed as outlined in *Table 4* below. Patients require observation at a minimum through the completion of Visit 4 (6 hours post-infusion). Patients may be admitted and observed overnight at the discretion of the PI. If the subject is an in-patient on Days 3-5, he/she should be assessed and samples collected as described in Table 4.

All patients in each cohort will be evaluated for any signs of AEs, serious adverse events (SAEs) and serious adverse drug reactions (SADRs) after infusion.

Patient infusions cannot occur on the same day. Once an enrolled patient has been infused, he/she must reach Day 4 without a suspension or stopping rule (1.9.8 Stopping Rules and Procedures for Study) event being reported prior to a subsequent patient being infused. In addition, there will be at least a two-week interval between cohorts to allow an independent Data Monitoring Committee (DMC) to review all patients' accumulated safety data after visit Day 6 from Cohort 1 and then again after the last patient from Cohort 2 has completed visit Day 6 in order to recommend whether the study should advance to the next cohort. Refer to Appendix B-Flow Diagram of Study Events.

Table 2. Patient Cohort Assignment, Dose and Safety Margins

Cohort	No. of Infusions	Target Mean Particles per kg	Target Mean TGPU per kg	Estimated Total Vol. Infused based on a 70kg patient and a mean Thrombosomes conc. of 1.61 x 10^9 particles per ml with an associated 2800 TGPU per ml[1]	Safety Margin[2]	
					Particles infused per kg	TGPU infused per kg
1 (Patients 1-8)	1	9.45 x 10^7	165	4.1 ml	300	301
2 (Patients 9-16)	1	1.89 x 10^8	330	8.2 ml	150	150
3 (Patients 17-24)	1	3.78 x 10^8	660	16.4ml	75	75

[1]Doses will be adjusted per weight of each patient, Estimated Total Volume Infused based on a 70kg patient and a mean Thrombosomes concentration of 1.7 x 10^9 particles per ml with an associated 3400 TGPU. Example Total Dose in ml = (Weight in kg X (desired Dose in particle count or TGPU, specific for each cohort))/ Thrombosomes particle count or TGPU per ml provided with each lot of Thrombosomes. EXAMPLE for Cohort 1: 70 X (9.45 x 10^7)/1.7 x 10^9 per ml = 5.5ml
[2]Safety margin based on the single acute toxicity study in NZWR (MPI 1542-001)

1.9.2.2 Additional Hemostatic Therapy: All Cohorts

This product is not expected to increase the platelet corrected count increment (CCI). The infusion of platelets for six hours prior and one hour after infusion of Thrombosomes is

restricted. However, at any time, if the patient's clinical bleeding remains unchanged or deteriorates with additional or worsening bleeding, the patient's physician(s) may transfuse the patient with blood products, hemostatic agents, or coagulation factors without limitation. The study patient will be followed for safety data for 30 (+2) days post-infusion of the dose of Thrombosomes.

1.9.3 Assessment of Bleeding: Using WHO Bleeding Score

Use of the WHO (World Health Organization) Bleeding Assessment will provide a standardized approach, across multiple clinical sites, in order to determine study eligibility, for assessing a patient's bleeding during the clinical trial, and for assessing the effect of Thrombosomes (if any) on bleeding. Study personnel conducting the assessment will be trained on the assessment and will be authorized by the PI to perform the assessment. This authorization will be documented on the Authorities and Responsibilities Log. The location of bleeding for all bleeding sites will be assessed by WHO grade during study at screening, (re-screening, if applicable) baseline, 1 hour, 6 hours, 24 hours post-infusion and 6 days post-infusion. In some instances, a bleeding site may not be able to be reassessed post-infusion due to the need for an invasive procedure or other procedure that would add additional risk for the subject. The protocol does not require subjects to undergo medically unnecessary procedures (or risks) only in order to perform post-infusion WHO bleeding assessments. Subjects who are transfused with red cells to treat anemia due to their underlying disease (and not because of bleeding) will not be assessed as having WHO grade 3 bleeding. Anemia from underlying disease will be designated if there is evidence of bone marrow suppression indicated by at least two of the following: leukopenia, thrombocytopenia, or reticulocytopenia; and absence of WHO grade 2 bleeding in the prior 24 hours. For designation of WHO grade 3 bleeding, red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding. (see Table 4. Schedule of Events for timing of WHO bleeding assessments). The same person must perform assessment of pre-infusion and 1-hour post-infusion time points.

To assess bleeding and determine the WHO Bleeding Score, the patient will be interviewed, a physical examination will be performed, and the patient's chart will be reviewed. The WHO Bleeding Score will be determined using Appendix A- Modified WHO Bleeding Score.

1.9.4 Blinding

This is an open-label safety study.

1.9.5 Duration of Patient Participation and Study

The duration of the patient's participation on the study is expected to be approximately 4-8 weeks. The time from first patient first visit to last patient last visit is expected to be 18 months.

1.9.6 Patient Compensation

Patients may or may not be compensated for participation in study. If compensated, the total should not exceed $1000.00, for time, parking and transportation costs during visits. See Table 3.

Table 3. Proposed Patient Compensation		
Visit No.	Type of Contact	Cohorts 1, 2 and 3
1	Screening	$200
2	Infusion Visit	$200
9	Day 6	$400
10	Follow-up 30-day visit	$200
	Total	$1000

1.9.7 Cohort Study Schedule

The assignment of treatment dose will be determined in sequential order, as shown in Table 2. Patients in Cohorts 2 through 3 will not receive infusion of study material until all eight patients in the previous cohort have received infusion of study treatments and have been observed through the completion of follow up visit Day 6, and the study data has been reviewed by one of the study investigators, the medical monitor, and the DMC. The DMC will meet before initiation of the study in order to approve a charter that will determine the process and schedule for reviewing the safety data, determination of serious adverse events, and the appropriate stopping rules for the study.

1.9.8 Stopping Rules and Procedures for Study

Suspension Rules

If an SAE is reported to the Sponsor that:

1. the investigator believes is possibly, probably, or definitely related to the use of the product (As defined in 1.22.6.1 Definition of Terms), and
2. does not meet the stopping rules criteria for SAEs listed below, then the Sponsor will confirm relatedness and suspend enrollment and infusion of patients in the study until further evaluation of the SAE is completed. The independent DMC will meet ad hoc to review the results of the event(s) with the Medical Monitor and PI who treated the patient. The DMC will then determine causality and recommend whether the study should either proceed without changes, proceed with modifications, or not proceed. See 1.22.6.4 Adverse Event Reporting for reporting of serious adverse events. Safety reports will be provided to FDA in accordance with 21 CFR 312.32.

Stopping Rules

The Sponsor will stop enrollment into the study if an SAE of death, thrombotic or embolic event, acute lung injury or anaphylaxis occurs that is directly (probably or definite) related to the product within 48 hours of infusion of Thrombosomes (except for anaphylaxis within 4 hours). If the study is stopped, the study will be restarted only after a complete review of the data is completed by the medical monitor, all PIs and the independent DMC, and it is determined that there is reasonable doubt that the event is related to the product. Safety reports will be provided to FDA in accordance with 21 CFR 312.32.

The following definitions will be used to characterize specific stopping rule SAEs:

- Thrombotic or embolic event (including myocardial infarction, pulmonary embolism, and venous thromboembolism [defined in Appendix C- Definition of Myocardial Infarction and Appendix E- DVT and PE Algorithm Pages from ICSI Guideline, respectively], or stroke [including transient ischemic attack]). A minor catheter thrombosis is not included in this category, or
- Pulmonary adverse event of acute lung injury (ALI) (defined in Appendix D- Definition of ALI), or
- Anaphylaxis (defined in Appendix G – Modified Definition of Anaphylaxis)

An SAE will be considered potentially attributable to the product if there is a high degree of certainty that 1) a relationship to a Thrombosomes infusion exists, 2) there is a reasonable temporal association, and 3) the event cannot be explained by known characteristics of the patient's clinical state or factors including other therapy. For an SAE to be considered to be definitely related to a Thrombosomes infusion, an association exists between the receipt of an investigational product and the event, and an association to other factors has been ruled out (See 1.22.6.2 Relationship to Investigational Product for definitions to determine causality).

1.9.9 Safety Endpoints

Primary: The occurrence and frequency of AEs, SAEs, and thromboembolic events as determined by clinical signs and symptoms, physical exam including neurological assessment, and laboratory studies.

Secondary:

- Describe the effect of increasing doses of allogeneic Thrombosomes on bleeding including changes in WHO bleeding grade.
- Describe the effect of increasing doses of allogeneic Thrombosomes on coagulation measures.

1.10 Study Population

1.10.1 Patient Numbers

Approximate number of patients screened: 120

Approximate number of patients consented: 60

Approximate number of patients enrolled: 30

Maximum Number of Patients Completed: 24 (8 patients in Cohorts 1-3)

Evaluable patients: 24

A patient is evaluable if they have completed their Day 6 follow up for Cohorts 1- 3.

1.10.2 Target Population

Patients will be screened as they are identified by the clinical trial site. Patients will be selected and approved for inclusion by the Principal Investigator based on inclusion/exclusion criteria as specified in 1.11 Inclusion /Exclusion Criteria of the study protocol, without any limitations to gender or ethnicity.

1.11 Inclusion /Exclusion Criteria

1.11.1 Inclusion Criteria

1. Males and non-pregnant/non-breastfeeding females at least 18 - 74 years of age.
2. Ability to comprehend the study procedures and signed informed consent.
3. Diagnosed with any the following: acute leukemia (ALL or AML), myelodysplasia, aplasia, and/or therapy (chemotherapy or radiation) induced bone marrow aplasia or hypoplasia with thrombocytopenia (see #6 below) for a minimum of 2 days. Patients who have received either autologous or allogeneic bone marrow transplant, peripheral, or cord blood stem cells may be enrolled *if* they do not have chronic or acute graft-versus-host disease (GVHD).
4. WHO Grade 1 (subset) or 2 bleeding or at risk for same within 4 weeks of screening. Subset of patients with Grade 1 bleeding are those who have either epistaxis, hematuria, oral petechiae, oropharyngeal bleeding, or bleeding at invasive or other wound sites. WHO Grades 0, 3 or 4 are not inclusion criteria for eligibility.
5. If not hospitalized, willing to be observed in a clinic up to the 6-hour post-infusion time point. Patients may be admitted and observed in the hospital overnight at the discretion of the PI.
6. Thrombocytopenia with platelet count $\geq$ 5,000/ µL and $\leq$ 70,000/µL.
7. Has permanent address and phone/email for contact and notifications, and available for the duration of the trial, which is expected to be a maximum of 8 weeks.
8. Agrees to not take any nonsteroidal inflammatory drugs within 5 days prior to infusion and during the 6 Day study follow-up period.
9. Agrees to not take any aspirin or aspirin containing drugs within 5 days prior to infusion and during the 6 Day study follow-up period.

10. Agrees to not take any COX-2 inhibitor drugs within 5 days prior to infusion and during the 6 Day study follow-up period.
11. Female patients must have a negative pregnancy test prior to enrollment and during study. Women who are postmenopausal for at least 1 year (>12 months since last menses) or are surgically sterilized do not require this test.
12. Females of childbearing potential should either be surgically sterile (hysterectomy or tubal ligation) or should use an effective, medically accepted contraceptive regimen. An effective method of birth control is defined as those which result in a lower 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), abstinence, or vasectomized partner.

1.11.2 Exclusion Criteria

1. Medical diagnosis of acute or chronic DIC (not based on fibrin degradation products alone).
2. PT or aPTT > 1.3 times the upper limit of normal for the laboratory.
3. Past diagnosis of stroke or thromboembolic events including deep vein thrombosis (DVT), pulmonary embolism, venous or arterial thrombosis, blood clots, or transient ischemic attack (TIA), not to include central or peripheral line-related thrombosis.
4. History of major operative procedures that required general anesthesia in the past 2 weeks.
5. A history or diagnosis of immune thrombocytopenia, thrombotic thrombocytopenic purpura, or hemolytic uremic syndrome.
6. Known inherited disorder of coagulation or platelet function (by history).
7. Receiving active treatment with Plavix (clopidrogel bisulfate) or Ticlid (ticlopidine hydrochloride), or other platelet inhibiting therapy.
8. Receiving tranexamic acid or other antifibrinolytics within 48 hours prior to infusion.
9. Receiving active, inpatient treatment full anticoagulation therapy. Note: a heparin flush may be given daily and before and after blood draws to patients with a central line to keep the line patent. Prophylactic anticoagulation is not a contraindication.
10. History of persistent headaches or migraines. Persistent headaches are defined as the headache frequency is 15 or more days a month for longer than 3 months in the absence of organic pathology.[2]
11. History of an MI, stent placement, had valve replacement and/or repair.
12. For patients with an active acute infection, suspected infection, or a single oral temperature of greater than equal to 101°F or a temperature greater than equal to 100.4° F sustained over a one hour period [3] in the past 24 hours. Fever related either to the patient's underlying diagnosis (cancer or other neoplastic process) or to the treatment of that disease process is

[2] Silberstein SD, et al. Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology. 1996;47(4):871.
[3] Freifeld et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2011;52(4):e56-e93.

not an exclusion to study participation. Subjects receiving antibiotics either to treat an infection or as expectant treatment of a clinically-suspected infection are excluded from study enrollment until the infection is resolved or ruled out. Subjects receiving prophylactic antibiotics to prevent an infection are not excluded from study.

13. Systolic blood pressure greater than 160 mmHg or lower than 90 mmHg; or diastolic pressure higher than 100 mmHg.
14. Treatment with any investigational agent within one month before treatment infusion for this trial, other than for treatment of their underlying disease.
15. Unwilling or unable to comply with the requirements of this protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the patient's return for follow-up visits on schedule as determined by the investigator.
16. Other unspecified reasons that, in the opinion of the Investigator or Medical Monitor, make the patient unsuitable for enrollment.
17. Patient is institutionalized because of legal or regulatory order.

1.11.3 Inclusion of Women and Minorities

The NIH Revitalization Act of 1993, PL 103-43, signed into law on June 10, 1993, directed the NIH to establish guidelines for inclusion of women and minorities in clinical research. It is believed that gender or racial differences will not have an effect on study outcomes, and therefore, the inclusion of women and minorities for this proposed clinical trial is not limited.

1.12 Recruitment Process

Patients will be recruited consecutively as they volunteer and as they meet the eligibility criteria and study timelines.

1.13 Sample Size Justification

For this Phase 1 dose escalation study (Cohorts 1 through 3), there is no statistical basis for the selection of the sample size. The sample size, 8 patients per cohort, was selected to provide a reasonable balance in order to assess safety while minimizing the number of patients potentially at risk. Further details will be given in 1.16 Data Analysis.

1.14 Informed Consent Process

Per 21 CFR Part 50 and 45 CFR Part 46, this clinical trial will require Informed Consent of each patient prior to participation. The informed consent form (original and any amended forms) will be reviewed and approved by IRBs. If acceptable, a central IRB will be designated for use by all participating sites, involved in the conduct of this clinical trial. Additionally, HIPAA Authorizations will be obtained as required.

The informed consenting interview process will be conducted during Visit 1 prior to patient screening activities. Potential patients are provided consent material ahead of time for their review. A member of the research team will review the informed consent form, in a factual

manner, with the individual, in a private area of the study site. The potential patient is allowed time to read the informed consent and then given an opportunity to ask questions. They are given ample time and left alone for as long as is needed before signing the informed consent. A research team member is in the area close-by and the Principal Investigator (PI) (or sub-investigator) is available via phone to answer any questions.

After the potential patients have read the consent, a member of the research team asks the individual whether they have any other questions. It is reiterated during the consent process that they can withdraw from the study at any time. The PI's phone is included in the Informed Consent Form in case they have any questions after signing the informed consent.

The research team member will note any lack of mental capability during the review of the consent with the patient and/or during the question and answer section of the process. If there are any concerns noted by the research team member, they will contact the PI (or sub-investigator) and discuss. The final decision regarding this requirement will be made by the PI (or sub-investigator), after the PI (or sub-investigator) has either:

- Heard clear and convincing information from the research team member that the patient does not meet an entry criterion, or
- Directly interviewed the patient to determine whether entry criteria are met.

As described in additional sections of this Study Protocol, as informed consent is an ongoing process, the interview process at the beginning of each study visit will re-address the information presented during the Informed Consent interview with the intention to confirm the volunteer's acceptance of continued participation. Verbal consent to continue study participation will be obtained prior to additional study procedures performed at that particular study visit.

Ample time and opportunity will be provided for a question and answer session to ensure that the patient can make an informed decision as to whether the research project is of interest. The patient will be encouraged to consult with family, friends or other counsel prior to choosing to participate in the study.

The Informed Consent Form will be initialed (as required by the IRB), signed and dated by the patient and witnessed and dated by the person conducting the consent interview. A signed copy of the consent form will be offered to the patient with the original form kept in study records.

1.15 Study Procedure

Patient case report form information will be prepared and provided to the investigational site, outlining the inclusion/exclusion criteria, physical exams, sample collections, and other interventions for each visit. Table 4 on the following pages provides the schedule of the evaluations for each patient.

Table 4. Schedule of Events

Evaluation	Initial Screen	Rescreen (if applicable[1])	Day 1[2] Base Line -2 hr pre-infusion	1 hr post infusion ± 15min	6 hr post -1 or +2 hr	Day 2 24 hr post ± 3 hr	If hospitalized			Day 6 (+ 4 days)	Day 30 (+2 days) (by phone)
							Day 3	Day 4	Day 5		
Visit #	1	1A	2	3	4	5	6	7	8	9	10
Sign ICF	X										
Verbal reconfirmation of informed consent		X	X	X	X	X	X	X	X	X	X
History and complete physical exam[4]	X										
WHO assessment	X	X	X	X	X	X				X	
Abbreviated physical exam[5]		X	X	X	X	X				X	
Pregnancy test (serum or urine)-applicable females only	X	X									
Concomitant medications (Medications, OTC Remedies, Herbal Preparations,	X	X	X	X	X	X	X	X	X	X	

Evaluation	Initial Screen	Rescreen (if applicable[1])	Day 1[2] Base Line -2 hr pre-infusion	1 hr post infusion ± 15min	6 hr post -1 or +2 hr	Day 2 24 hr post ± 3 hr	If hospitalized			Day 6 (+ 4 days)	Day 30 (+2 days) (by phone)
							Day 3	Day 4	Day 5		
Vitamins, Supplements and IV fluids)											
Record transfused blood products[6]	X	X	X	X	X	X	X	X	X	X	
Infusion			X								
Vital signs (pulse, BP, RR, temp)	X	X	X	Prior to infusion and then every 15 min ±5 min after the start of infusion until 2 hrs; continue every hour ±5 min until 4 hrs, then at 6 hrs, and 24 hrs post infusion.						X	
Pulse-Ox			X	Continuously monitor while monitoring for vital signs; record at same time points as for vital signs above.							
Monitor for AE			X	Prior to infusion and then every 15 min ±5 min after the start of infusion until 2 hrs; continue every hour ±5 min until 4 hrs, then at 6 hrs, and 24 hrs post infusion, ±10 mins for all other time points. Daily until discharged or Day 6.			X	X	X	X	X[3]
12-Lead EKG	X		X[9]		X						

Evaluation	Initial Screen	Rescreen (if applicable[1])	Day 1[2] Base Line -2 hr pre-infusion	1 hr post infusion ± 15min	6 hr post -1 or +2 hr	Day 2 24 hr post ± 3 hr	If hospitalized			Day 6 (+ 4 days)	Day 30 (+2 days) (by phone)
							Day 3	Day 4	Day 5		
Hematology CBC[6,7] (if blood products are transfused, then CBC pre and post transfusion)	X	X	X	X	X	X	Minimum is daily CBC			X	
ABO group, Rh type	X										
Coagulation Tests[8]: PT/INR, aPTT, D-dimer, Fibrinogen, TAT, PF 1+2, TEG or ROTEM, TGA	Only PT/INR, aPTT, D-dimer, Fibrinogen	Only PT/INR, aPTT, D-dimer, Fibrinogen	X	X	X	X					
Routine Chemistry: Na, K, Cl, CO2, Glucose, BUN, Creatinine, Albumin, Total Bili, Ca, AST, Alkaline Phosphatase, ALT, GGT, LDH, Total Cholesterol, Total Protein			X		X	X					
Special Chemistry hsTroponin I or T Assay			X		X	X					
Draw archive sample[10]	X									X	

Evaluation	Initial Screen	Rescreen (if applicable[1])	Day 1[2] Base Line -2 hr pre-infusion	1 hr post infusion ± 15min	6 hr post -1 or +2 hr	Day 2 24 hr post ± 3 hr	If hospitalized			Day 6 (+ 4 days)	Day 30 (+2 days) (by phone)
							Day 3	Day 4	Day 5		

[1] Rescreening performed on those patients who passed eligibility criteria, were not actively bleeding at time of initial screen, and started bleeding within 4 weeks. Patients who were initially screened within 4 days (+6 hrs) do not need to be re-screened except for WHO bleeding assessment and CBC.
[2] Baseline may occur on the same day (within 24 hours) as either Initial Screen or Rescreen. The WHO assessment, CBC and coagulation must be collected at baseline, not more than 2 hours prior to infusion. Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding.
[3] Chart review for SAEs (only) needs to include data from day 1 though Day 30 (+2 days). Phone call with patient is to confirm if the patient had an SAE or required emergency medical care at an outside facility.
[4] Complete physical exam to include height, weight, general assessment of health by history and medical exam including neurological exam. History to include previous transfusion with red blood cells, plasma and/or platelets.
[5] Abbreviated Physical Exam to include general appearance, cardiovascular, respiratory, extremities, abdomen and head and neck.
[6] In the event of the transfusion of a blood component after infusion of Thrombosomes on Days 1-6, CBC results are required from a sample collected within 8 hours or less prior to the transfusion and within 1-hour (+30 min) post transfusion.
[7] Daily CBC required, but ALL CBC data for each patient during the hospitalization phase through Day 6 must be collected and entered into the database.
[8] If TEG or ROTEM testing is available, include samples for the record.
[9] Repeat EKG if performed more than 4 days before infusion.
[10] For each of the time points that require archive samples, two 10 ml samples will be drawn; one for plasma (EDTA) and one for serum.

1.15.1 Measures to Protect Study Patients

- An emergency study contact number will be provided to all patients. If not hospitalized, patients will be advised to go to an emergency room if immediate attention is needed. They will be advised to tell the emergency room staff that they are in a clinical study.
- Each patient will be monitored for 30 (+2) days after infusion.
- Patients in Cohorts 2-3 will not receive infusion of study material until all eight patients in the previous cohort have received infusion of study material and been observed through the completion of visit Day 6, and the study data has been reviewed by one of the study investigators, the medical monitor, and the DMC.
- Stopping rules and DMC review processes have been established. See 1.9.8 Stopping Rules and Procedures for Study
- Adverse events, including clinical signs and symptoms, abnormal laboratory test results post-infusion, and events reported directly by patients will be documented on AE case report forms and reported by the PI to the sponsor as they are identified (see 1.22.6 Adverse Events and Unanticipated Problems).
- Because in vitro evaluation of Thrombosomes indicates some properties common to partially activated platelets, the PI is requested to be alert for signs/symptoms of vascular occlusions/thrombosis, including stroke, heart attack, peripheral vascular occlusion, anaphylaxis, and acute lung injury. Definitions for an MI, ALI and Anaphylaxis are presented in Appendix C- Definition of Myocardial Infarction, Appendix D- Definition of ALI, and Appendix G – Modified Definition of Anaphylaxis respectively. Algorithms from an ICSI guideline on the Diagnosis and Treatment of Venous Thromboembolism and Pulmonary Embolism are in Appendix E- DVT and PE Algorithm Pages from ICSI Guideline of this protocol and the complete guidance will be provided to the PI.[4]

1.15.2 Receipt and Storage of Thrombosomes

Thrombosomes will be shipped to the study site by Cellphire, Inc. Procedures will be established by which:

1. Thrombosomes are checked upon receipt to assure the packaging is intact, no seals are broken and the temperature range recorded on the internal monitoring device has not exceeded 40ºC.
2. Vial(s) of Thrombosomes will be stored at ambient temperature (not to exceed 40ºC) in a secure area for clinical supplies. The amount of product received, accepted into inventory and returned to the Sponsor will be entered into study records.
3. All reconstituted Thrombosomes will be retained at 4°C on site for at least 7 days after the infusion and be destroyed at the site as a biological material.
4. Unused, unopened vial(s) of Thrombosomes will be returned to Cellphire.

[4] https://www.icsi.org/_asset/5ldx9k/VTE0113.pdf

1.15.3 Drawing Blood Samples from Patients

The samples to be collected from the patient for this study are listed below. Blood will be collected according to policies at each site or central laboratory, in tubes and volumes per site specifications, and will be listed in the informed consent form for that site. For each of the timepoints that require archive samples, two 10 ml samples will be drawn; one for plasma (EDTA) and one for serum.

Blood Sample Requrements for All Cohorts Test(s) performed:

- Coagulation Panel
- Archive Sample
- Hematology: CBC
- Pregnancy (serum)
- Special Chemistry
- hs Troponin I or T
- Routine Chemistry

Note: A frozen archive sample will be retained at the site. Upon request by the Sponsor, archive samples will be shipped to the Sponsor. Archived samples will be destroyed by the Sponsor within 180 days after FDA review of the final study report. Archived samples will be used to repeat any one of the tests described in the protocol.

1.15.4 Instructions for Reconstitution and Administration of Thrombosomes

See Appendix F – Instructions for Reconstitution and Preparation of Thrombosomes – for instructions for reconstituting the vial(s) of Thrombosomes and preparing Thrombosomes doses for use. Study sites receiving, storing, preparing and administering Thrombosomes should be operating under BSL-2 workplace biosafety measures as applied in the blood establishment setting (AABB Technical Manual, 19th edition, 2017, Chapter 2, Facilities, Work Environment and Safety). Thrombosomes should be kept at room temperature and infused by IV within one hour of reconstitution. Use a Hemo-Nate® filter supplied by the Sponsor, in the administration of the product (see Appendix F – Instructions for Reconstitution and Preparation of Thrombosomes for Administration).[5]

To administer the study material in patients, the investigator may use the central or existing IV line if available. If not, obtain IV access in patient. Begin the administration of normal saline using an infusion administration set with a standard medication injection site. Check the identity

[5] Although preclinical, laboratory, and clinical testing to date do not suggest that Thrombosomes® need to be filtered during administration, the FDA has recommended the use of a blood filter for this study as a precautionary measure. Cellphire conducted studies of several FDA cleared blood filters with pore sizes from 18 to 150 microns. None of the filters tested affected the biologic or physical characteristics of Thrombosomes. The Hemo-Nate® Filter #4020009 (Utah Medical Products, Midvale, UT) has been selected for use in this clinical trial and will be supplied to sites by the sponsor. Selection was based on the material (stainless steel), low priming volume (0.7 ml), 18 micron size, and ease of use.

of the patient with the prepared label. Stop the normal saline infusion and begin administration of the predetermined dose of study material at the rate of 1ml/min through the medication injection site using a syringe infusion device capable of delivery at the required rate. After the infusion, begin administration of the normal saline and use approximately 25 ml to flush the line.

1.15.5 Blinding of Study Patients

This is an open label study and no blinding is required.

1.15.6 Unscheduled/ Emergency Follow-up Visits

Patients will be provided with a study number to call, in the event of emergency, but will be advised to go to an emergency room if immediate attention is needed. If a patient calls to request a physician follow-up for any health problem possibly related to the study at any time after infusion of Thrombosomes, the following procedure should be followed:

1.15.6.1 Non-emergent Unscheduled Patient Evaluation (minimum)

A. Perform a complete physical exam to include vitals (BP, pulse, RR and temperature) and general assessment of health and medications, and if an AE occurs, document on CRF. Assess patient for acute reactions to include coagulopathies, thromboses and delayed hemolytic transfusion reactions. Treat clinical symptoms and presentation according to standard of care. In addition, refer to the guidance provided on definitions for MI, Pulmonary Embolism, Anaphylaxis, ALI, and Venous Thromboembolism in Appendix C- Definition of Myocardial Infarction, Appendix D- Definition of ALI Adapted from NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol v2.4, Appendix E- DVT and PE Algorithm Pages from ICSI Guideline, and Appendix G – Modified Definition of Anaphylaxis if suspected.

B. Conduct patient interview to assess health and self-declared AE by the patient.

C. Obtain complete information on any adverse events and any medications used.

D. Perform appropriate testing (as determined by the PI) to determine the cause of the adverse event.

E. If hospitalization is required or extended, report to Cellphire as soon as possible, and complete the medical evaluation as needed.

1.15.6.2 Blood Sampling/Testing

A. Additional tests for evaluation and/or treatment of safety and/or laboratory events may occur. The additional tests will be determined by the patient's signs, symptoms or review of laboratory data, and will not be dictated by the protocol. A recommendation for the need for additional testing will be made by the patient's treating physician. The patient must agree to the additional tests before these tests can be performed.

B. Label all blood tubes following sites standard operating procedures (SOP) and patient study ID number, date, time and visit number.

C. Send samples for testing following site's SOP.

D. Complete Adverse Event Form that includes description of the event, relatedness, start date, stop date, medications used to treat and results of laboratory testing.

1.15.6.3 AE Evaluation

A. If necessary, consult with emergency physicians and obtain emergency medical treatment.

B. Schedule follow-up visits; frequency of these visits at the discretion of the Investigator.

C. Contact the Medical Monitor to assist with a full evaluation of any AE. See Section 1.22 Study Organization and Management Plan of this clinical protocol for AE and Serious Adverse Event (SAE) reporting information, if needed.

1.16 Data Analysis

Separate data summaries will be prepared for each cohort:

- Demographic and medical history data will be summarized. For quantitative variables, summaries will include the sample size, mean, median, standard deviation, minimum, and maximum. For qualitative variables summaries include the number and percent of patients for each outcome.
- Exploratory analyses will include the observed response and the change from baseline to each of the post-infusion time points for each of the laboratory tests (hematology, coagulation, platelet and chemistry). Additionally, summaries of the number and percent of patients with both a change of >5% from baseline and whose results are outside of reference ranges will be displayed. For quantitative variables summaries of the observed response and the change from baseline to each of the post-baseline time points will include the sample size, mean, median, standard deviation, minimum, and maximum. Additionally, for the change from baseline summaries, the statistical significance will be determined using either a t-test or the Wilcoxon Signed Rank test, as appropriate. Summaries for qualitative variables will include the number and percent of patients for each outcome.
- Incidence of AEs and SAEs per patient and by body system will be summarized showing the number and percent of patients for each outcome. Summaries will also be prepared by severity and relationship to treatment.
- Summaries of vital signs and clinical data including WHO bleeding scores will include the observed response and the change from baseline to each of the post-infusion time points for each of the variables. For quantitative variables summaries of the observed response and the change from baseline to each of the post-baseline time points will include the sample size, mean, median, standard deviation, minimum, and maximum. Additionally, for the change from baseline summaries, the statistical significance will be determined using either a t-test or the Wilcoxon Signed Rank test, as appropriate. Summaries for qualitative variables will include the number and percent of patients for each outcome.

A statistical analysis plan will be developed as part of the data analysis plan.

1.17 Data Management

Data will be gathered and managed by a fully qualified CRO. Electronic case report forms will be completed at the site and sent to the CRO where the data will be screened for typographical errors and then validated to check for logical errors. Errors found will be reviewed to determine if there is an error in the data or clarification from the site is required. Records will be retained by the CRO as required by CFR and guidance documents.

1.18 Risk Assessment

1.18.1 Foreseeable or Potential Risks

The following risks to participation of this clinical trial are outlined in the Table 5 below:

Table 5. Potential Study Risks

Trial Stage	Risks Identified
AEs Possibly Related or Related to Thrombosomes Infusion during Phase 1 Study No. 2011-1	• Prothrombin Level Increased (Elevated Prothrombin Fragment 1+2) • White Blood Cell Count Increased • Fibrin D-dimer Increased • Electrocardiogram T-wave Abnormal • Autoantibody Positive (Platelet Autoantibody)
AEs Associated with Blood Product Infusion including Platelet Infusion which may also be associated with Thrombosomes	• Hematoma or localized infection at the venipuncture site • Nausea/vomiting, dizziness/ fainting, seizures • Allergic reaction (flushing, itching, hives, abdominal cramps, difficulty breathing, chest pain, or bronchospasm, which may vary in severity from mild to life-threatening) • Difficulty breathing, chest pain, or bronchospasm, which may vary in severity from mild to life-threatening) • A minimal risk of cancer cannot be completely and definitely ruled out • Immune suppression • Infectious disease transmission • Cardiac failure • Noncardiac pulmonary edema • Stroke • Thrombocytopenia • Formation of platelet antibodies • Thrombosis – arterial or venous • Pulmonary Embolism • Heart attack • Death
Miscellaneous	• Breach of patient confidentiality

1.18.2 Potential Patient Risks for Special Vigilance by Investigator

See 1.15.1 Measures to Protect Study Patients.

1.18.3 Potential Risks to Study Personnel

Risks associated with the handling of blood and blood products are expected for this clinical trial. All study personnel will be trained in good clinical practices, including Universal Precautions, in the sampling and handling of blood and body fluids that are collected, processed or tested during the course of this clinical trial. The Investigator will be responsible for ensuring that staff who will handle blood or body fluids be trained in Bloodborne Pathogens, Infection Control and Universal Precautions.

1.18.4 Risk Management and Emergency Response

1.18.4.1 Pregnancy

Risks associated with use of this investigational product are unknown. Therefore, the inclusion/exclusion criteria require that women of childbearing potential must have a negative pregnancy test and must agree to practice a medically acceptable contraception regimen throughout the participation in the clinical trial, (which can be up to 8 weeks). An effective method of birth control is defined as those which result in a lower 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), abstinence or vasectomized partner. Women who are postmenopausal for at least 1 year (> 12 months since last menses) or are surgically sterilized also meet the inclusion criteria.

Should the patient become pregnant during the course of the study, she will be withdrawn from the study. The PI should have a discussion with the patient on whether the patient wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. The PI must distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the patient's information. If a patient withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described above, the investigator must obtain the patient's informed consent for this limited participation in the study.[6]

1.18.4.2 Risk Management

As this is a dose escalation study design, infusions must take place according to cohort assignment. Patients in Cohorts 2 and 3 will not receive infusion of study material until all eight patients in the previous cohort have received infusion of study material and been observed through the completion of visit Day 6 and the study data has been reviewed by one of the study investigators, the medical monitor, and the DMC. Stopping rules for select safety events are also part of the study protocol. See 1.9.8 Stopping Rules and Procedures for Study.

[6] From the FDA Guidance, "Guidance for Sponsors, Clinical Investigators, and IRBs" Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials (2008)

Research staff must be trained in the venipuncture, sample collection and infusion procedures described in this protocol and in the recognition and treatment of known potential side effects of these procedures.

1.18.4.3 Emergency Care and Treatment

Medical oversight must be available to the patient as required. Follow-up blood sample draws will be conducted at site.

1.18.5 Stopping Criteria and DMC Review

See 1.9.8 Stopping Rules and Procedures for Study.

1.18.6 Potential Benefits

There are no definitive benefits to study patients participating in the study. Thrombosomes may have efficacy to reduce bleeding; however, it is not now known whether this potential benefit is better than, equal or less than the efficacy of apheresis platelets.

1.19 Study Personnel

1.19.1 Key Study Personnel

The roles and responsibilities of key study personnel will be assigned and documented using a local form for "Authorized Signatures and Delegation of Responsibilities Log" prior to the trial initiation.

1.19.2 Conflict of Interest

The Principal Investigator and key staff will provide in writing and retain records of all financial information and all other records required under applicable FDA regulations and IRB requirements, including but not limited to 21 CFR Part 54.6. The Investigator and key staff will be required to authorize the Sponsor, the FDA, and other government agencies to have access to, copy and verify these records. The Sponsor will be notified immediately in writing if any of the information disclosed changes during such time period. Investigator Financial Disclosure Form will be used to facilitate disclosure.

If conflicts of interest do exist and are disclosed, efforts to mitigate the impact of conflicts of interest will be undertaken. Information regarding conflicts of interest will be disclosed to volunteers as part of the consent form for the study.

1.20 Medical Monitoring

Qualified medical monitoring will be performed by Joan C. Pehta, MD. The Medical Monitor will review all adverse events, unanticipated problems involving risk to patients or others (unexpected serious adverse drug reactions), serious adverse events and all deaths associated with the protocol and provide an unbiased written report of the event to Cellphire. At a minimum, the Medical Monitor will comment on the outcomes of the event or problem and, in

the case of an unexpected serious adverse drug reaction or death, comment on the relationship to participating in the study and study products. The Medical Monitor will also indicate whether he/she concurs with the details of the report provided by the study Investigator. Reports for serious, unexpected adverse events determined by the Medical Monitor to be possibly, probably or definitely related to study drug including reports of events resulting in death will be promptly forwarded to the FDA and the IRB of record.

Safety reports (as defined by 21 CRF 312.32) will additionally be provided to the FDA as part of study records.

1.21 Study Monitoring and Auditing

Cellphire, Inc. or its designee, is responsible for the monitoring and auditing of the clinical study conducted at investigator sites according to Good Clinical Practices and FDA regulations.

Additionally, employees of FDA, BARDA, the IRB of record or other regulatory authorities may audit or observe an audit of the study during a visit at the Investigator's site.

For all monitoring or auditing visits, it is expected that the Investigator facilitate the processes by providing time, adequate facilities, study and patient records, and personnel necessary to support the monitoring or auditing process.

1.22 Study Organization and Management Plan

1.22.1 Study Management

Training at the clinical site will be provided by the study Sponsor and designees prior to commencement of the clinical trial. Training activities will include: informed consenting procedures specific to the study; enrollment procedures; randomization of patients; modified WHO bleeding assessments; investigational product labeling, storage requirements, reconstitution, use and accountability; data collection (CRF form), data query procedures and data corrections; reporting of adverse events; and study monitoring requirements. All training elements will be covered with respect to observation of Good Clinical Practices.

1.22.2 Study Timeline

The estimated timeline for conducting this Phase I IND study is approximately 12 months from first patient enrollment.

1.22.3 Patient Withdrawal

Patients may discontinue participation in the study at any time without penalty or loss of benefits to which the patient is otherwise entitled. If the patient *indicates* a desire to withdraw from the study, consideration must be made as to the timing of the patient's decision versus the study procedures performed to date. Table 6 indicates the appropriate planned follow-up given each stage of the study.

Table 6. Requirements Following Patient Withdrawal		
Visit Number	**Procedures**	**Follow-up Required**
1or 1A	Initial screening or Rescreening	None
2 through final visit	Infusion	• If patient was not infused prior to withdrawing, complete the withdrawal form. • If infusion was initiated before withdrawal, discontinue the infusion, and complete the final exam and blood draws to assess for safety. Request that patient return for follow-up visits as scheduled to ensure safety. Minimally, obtain patient contact information and perform follow-up phone calls if the patient doesn't come for visits. Provide clinic contact information for procedure-related concerns or patient-initiated follow-up. • If infusion was completed before withdrawal, complete the final exam and blood draws to assess for safety. Request that patient return for follow-up visits as scheduled to ensure safety. Minimally, obtain patient contact information and perform follow-up phone calls if the patient doesn't come for visits. Provide clinic contact information for procedure-related concerns or patient-initiated follow-up.

Patient interview will be documented by a written record of the interview and patient responses, signed and witnessed by the participant and staff conducting the exit interview at the time of withdrawal.

The anticipated circumstances under which the patient's participation may be terminated by the Investigator are indicated as follows:

- Non-compliance (*e.g.*, no-show for scheduled visit, impairment due to drugs/alcohol, agitation or disruption during visit, inability to follow clinic-established rules concerning conduct)
- Safety issues (*e.g.*, patient does not meet inclusion criteria for ongoing stages of the study, clinic safety due to unacceptable conduct, study cancelled due to product safety)
- Sponsor-initiated study termination
- Investigator-initiated study termination
- IRB of record or FDA study termination

1.22.4 Protocol Modifications

Modifications to the research protocol (other than purely administrative changes) including any modifications that could potentially increase risk to patients must be submitted to the IRB, for

approval prior to implementation and submitted to FDA. Some examples of major modifications include a change in Investigator, addition of a research site, changes in study design and addition or widening of a study population.

Protocol modification other than administrative (changes in phone, addresses, spelling errors, etc.) will be submitted to the central or institutional IRB for review as well as to the FDA.

1.22.5 Protocol Deviations

1.22.5.1 Anticipated Deviations

Anticipated deviations are events that the Investigator anticipates or would like to be aware of prior to when they occur. See Table 7. An anticipated deviation must be reported using the EDC and discussed with the Sponsor prior to its occurrence. The Sponsor will assess the requested deviation for a possible effect on safety or rights of the patient or on the impact to study data or quality. The Medical Monitor will be consulted for opinion regarding anticipated deviations.

Table 7. Protocol Deviations (Anticipated)

Anticipated Deviations	Action Required
Patient does not return for scheduled visit post-infusion follow-up	Attempt to call at least two times. Document call times on phone log. Contact by registered letter if still unresponsive.
Visit dates outside of range specified in protocol	Note correct time/day on CRF and keep a log of same for entire study

1.22.5.2 Unanticipated Deviations

Unanticipated deviations are events not foreseen by the Investigator, and typically reflect reactions or judgment calls by the Investigator. Unanticipated deviations can also result from Investigator or staff error. An unanticipated deviation must be reported to the Sponsor using the EDC as soon as it is recognized. Report can primarily be verbal; however, it must be followed with written documentation. The written report must explain the reason and rationale for the deviation, if the deviation affects the safety or rights of the patient or additional patients and recommended corrective actions. The Sponsor will formulate an appropriate follow-up plan (e.g., additional site training). The Medical Monitor may be consulted for opinion regarding unanticipated deviations. Any deviation to the protocol will be documented in study records. Deviations that may have an effect on the safety or rights of the patient or the integrity of the study must be promptly reported to the IRB of record. Documentation of any actions taken by the IRB of record related to the deviation report will be provided to the study Sponsor.

1.22.6 Adverse Events and Unanticipated Problems

1.22.6.1 Definition of Terms

A. Adverse Event (or Adverse Experience):

Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An

adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An abnormal laboratory finding that requires medical or surgical intervention or leads to study treatment interruption or discontinuation must be recorded as an AE (or SAE, if applicable). If the changes from baseline are mild and in the opinion of the investigator not clinically significant, the event is not considered an AE, however, the investigator should continue to carefully monitor the values. Laboratory tests may be repeated, as clinically indicated, without prior approval by Sponsor or Medical Monitor. Special attention must be paid to the results of coagulation parameter results not within reference ranges.

B. Adverse Drug Reaction (ADR):

In the clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, *i.e.,* the relationship cannot be ruled out.

C. Unexpected ADR:

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

D. SAE or ADR:

An adverse event that occurs during a clinical investigation and if suspected to be medicinal product-related (adverse drug reactions), and might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms. These events result in:

- Death.
- Life-threatening situation (patient is at immediate risk of death).
- In-patient hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs).
- Prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in the offspring of a patient who received study drug.
- Other: important medical events that may not be immediately life- threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are as follows:

- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

E. Clarification of SAE

- Death is an outcome of an AE, and not an AE in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study treatment(s).
- All deaths, regardless of cause or relationship, must be reported for patients on study and for deaths occurring within 30 (+2) days of last study treatment or within 30 (+2) days of last study evaluation, whichever is longer.
- "Occurring at any dose" does not imply that the patient is receiving study treatment at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- "In-patient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The Investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the predefined outcomes described above.

1.22.6.2 Relationship to Investigational Product

The site PI must assign a relationship of each AE to the receipt of the investigational product. The PI will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness, or concomitant medications. The following guidelines should be used to assess the relationship of an AE to study product administration and **ONLY THE INVESTIGATOR (QUALIFIED MD/DO) CAN MAKE THIS DETERMINATION:**

- Not related: No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.

- Unlikely: Likely unrelated to the investigational product. Likely to be related to factors other than investigational product, but cannot be ruled out with certainty.
- Possibly: An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the patient's clinical status or underlying factors including other therapy.
- Probably: There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the patient's clinical state or factors including other therapy.
- Definite: An association exists between the receipt of an investigational product and the event. Any association to other factors has been ruled out.

1.22.6.3 Severity Assessment

All AEs will be assessed for severity by the PI. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. The CDC National Healthcare Safety Network Hemovigilance Module criteria will be used to help define transfusion-related events. The NCI Common Terminology Criteria (CTCAE version 4.0, June 14, 2010) for toxicity grade will be used to assign the severity for all AEs (transfusion and non-transfusion related) (HHS-2010). The criteria below may be used for any symptom not included in the grading scale. Any Grade 4 (life-threatening) or Grade 5 (fatal) AE must be reported as an SAE.

- Mild Grade 1 Does not interfere with routine activities Minimal level of discomfort
- Moderate Grade 2 Interferes with routine activities Moderate level of discomfort
- Severe Grade 3 Unable to perform routine activities Significant level of discomfort
- Life-threatening Grade 4 Hospitalization or emergency room visit for potentially life-threatening event
- Fatal Grade 5 Results in Death

1.22.6.4 Adverse Event Reporting

The PI is responsible for reporting all adverse events or unanticipated events to the local IRB, as required, and to Cellphire on a schedule related to the seriousness of the event. A case report form will be provided for these reports. Events that meet the definition of "serious," including unexpected adverse reactions (SUSARs), thrombotic adverse events, and deaths as described above, must be entered into the electronic data capture (EDC).

All SAEs must be reported to Cellphire and or Sponsor's designee, the Contract Research Organization (CRO), in the EDC within 24 hours of the Investigator becoming aware of the SAE. If the site is unable to enter the event information into EDC for any reason the site can alternatively complete the paper SAE Form, which should be faxed/emailed within 24 hours from the point in time when the investigator becomes aware of the SAE. In addition, all SAEs that occur up to and including 30 days after administration of Thrombosomes must be reported to

the Sponsor or Sponsor's designee within 24 hours from when the investigator becomes aware of the SAE.

To report an SAE, sites will enter the SAE information into the EDC or complete an SAE Report and send the SAE report to the CRO, Clinipace Worldwide, Inc.

The investigator must report new significant follow-up information for these events to the Sponsor's designee immediately (i.e., no more than 24 hours after becoming aware of the information).

Cellphire is responsible for reporting to the DMC and the FDA according to the charter, policies and applicable guidance or regulations.

Adverse Event Reporting Contacts

- Medical Monitor Contact: Joan C. Pehta, MD
  Office: 203 972 0481
  Cell: 203 536 7604
  Fax: 203 972 6705
  Email: JCPehta@aol.com

- Safety Reporting Contact: Clinipace Worldwide
  Fax: 919 573 0332
  Email: safetygroup@clinipace.com

- Cellphire Contact: G. Michael Fitzpatrick, PhD
  Office: 240 268 2470
  Cell: 301 525 6885
  Fax: 240 268 1145
  Email: mfitzpatrick@cellphire.com

1.22.7 Study Forms and Recording of Information

It is the Investigator's obligation to ensure that all Case Report Forms and data collection instruments are accurate and complete. All study forms must be signed and dated by the Principal Investigator or designee, to attest that they are an accurate and complete record. A Signature and Delegation log will be completed and signed by the Principal Investigator during the training/initiation visit and kept as a part of the study records.

1.22.8 Continuing Review and Reporting

The IRB of record requires approval of all protocol amendments, acceptance of continuing review reports, reporting of protocol deviations and unexpected serious adverse drug reactions. A copy of the approved continuing review report and the local IRB approval notification may be submitted by Cellphire to the responsible Biomedical Advanced research and Development Authority (BARDA) representative or the Contracting Officer's Representative (COR) as

appropriate. A copy of the final report and local IRB approval notification may be submitted to BARDA as soon as these documents become available.

Additionally, BARDA requires reporting of any pending compliance inspection/visit by the FDA, OHRP or other government agency concerning the research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the responsible BARDA representative or the COR as appropriate.

1.22.9 Applicable Regulatory Requirements

The conduct of this clinical trial will adhere to the following regulations:

- 21 CFR Parts 11, 50, 54, 56, 312
- 21 CFR 600-640 subparts A, D, G
- 45 CFR 46, Protection of Human Subjects
- 32 CFR 219.103, Assurance of Compliance for the Protection of Human Research Subjects
- Health Insurance Portability and Accountability Act of 1996 (HIPAA)
- FDA guideline "Good Clinical Practice: Consolidated Guideline" (ICH E6)

1.22.10 Confidentiality and Disposition of Records

1.22.10.1 Confidentiality of Study Information

This collaborative clinical investigation is a CONFIDENTIAL study performed by the Investigator and Cellphire, Inc. No information concerning the nature and performance of this study, the results of this study, or the evaluation of those results is to be disclosed without the written approval of Cellphire, Inc. It is expected that any proprietary information provided by Cellphire, Inc will be maintained by the Principal Investigator in a secure fashion to restrict access only to authorized personnel.

The primary source document for the study will be the study participant's research records. The research records will be considered the source documents for the purposes of auditing the study. Any information that would identify the patient will be kept in a secure location at the clinical site. Secure is defined as access only to members of the research team by method of a locked location with key access only available to limited research team members. Applicable source data will be entered to approved CRFs. All data will be de-identified and a copy of each completed CRF will be retained at the Sponsor according to 21CFR 312.57(c), record retention. At, the study site the data will be kept in secure storage for the required length of time as indicated in 21CFR 312.62(c), record retention.

1.22.10.2 Confidentiality of Patient Information

Cellphire, Inc or its designees, employees of FDA or other regulatory authorities, the IRB of record, may consult source documents in order to verify data, and as such, confidentiality cannot be guaranteed. The study records and laboratory specimens will be stored in a confidential manner and will be coded to protect the patient's confidentiality.

1.22.11 Security of Investigational Products

Investigational products will be stored within a secure, limited access enclosure at each investigative site. Access will be provided to only the Investigator and his designee(s) responsible for product storage, preparation, tracking and usage. Investigational product accountability will be maintained.

1.22.12 Shipping of Specimens

It is the Investigator's responsibility to ensure that there are trained personnel available to ship diagnostic specimens following DOT/IATA regulations and site's Standard Operating Procedures.

1.22.13 Clinical Trial Registration

Information concerning this Phase I clinical trial will be registered on www.clinicaltrials.gov prior to study initiation pursuant to US Public Law 110-85, Title VIII, and Section 801.

1.22.14 Investigator Signature Page

I have read the attached protocol entitled, "A Phase I, Multi-Center, Open-Label, Dose Escalation Study of Allogeneic Thrombosomes® in Bleeding Thrombocytopenic Patients in Three Cohorts" **Version 2.0,** dated **18 October 2018**, and agree to conduct the study according to the provisions described therein.

I agree to comply with the International Conference on Harmonization Guideline on Good Clinical Practice and applicable Food and Drug Administration (FDA) regulations set forth in 21 CFR Parts 50, 54, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior consent of Cellphire, Inc.

The signature below constitutes my agreement to conduct the study according to the provisions of this protocol the contents of this protocol.

_____

Principal Investigator Date

_____

Title

_____

Institution

Appendix A- Modified WHO Bleeding Score

(Adapted from Supplement from Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic transfusions and prevention of hemorrhage. N Engl J Med 2010;362:600-13)

	Grade 1	Grade 2	Grade 3
Oral and nasal	• **Oropharyngeal bleeding – total duration of all episodes in previous 24 hours ≤ 30 minutes*** • **Petechiae of oral mucosa** • **Epistaxis – total duration of all episodes in previous 24 hours ≤ 30 minutes***	• Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* • Epistaxis – total duration of all episodes in previous 24 hours >30 minutes*	• Any bleeding requiring RBC transfusion over routine transfusion needs**
Skin, soft tissue, musculoskeletal	• Petechiae of skin • Purpura ≤ 1 inch diameter • One or more spontaneous hematomas in the soft tissue or muscle > 1 inch	• Purpura > 1 inch diameter • Spontaneous hematoma in deeper tissues • Joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	• Any bleeding requiring RBC transfusion over routine transfusion needs**
Gastrointestinal	• Positive stool occult blood test	• Melanotic stool • Hematochezia – visible red blood mixed in stool, not requiring a transfusion • Hematemesis – Grossly visible blood in emesis or in nasogastric drainage tube (not related or secondary to swallowed blood)	• Any bleeding requiring RBC transfusion over routine transfusion needs**
Genitourinary	• **Any biochemical or microscopic Hb/RBCs without red urine** • Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle OR Bleeding heavier than normal OR Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) with spotting	• Gross/visible hematuria without need for transfusion • Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle OR Bleeding heavier than normal OR • Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) more than spotting	• Any bleeding requiring RBC transfusion over routine transfusion needs**
Pulmonary		• Hemoptysis – Visible blood • Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding)	• Any bleeding requiring RBC transfusion over routine transfusion needs**
Body Cavity		• Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) short of criteria for Grade 3 or 4	• Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene

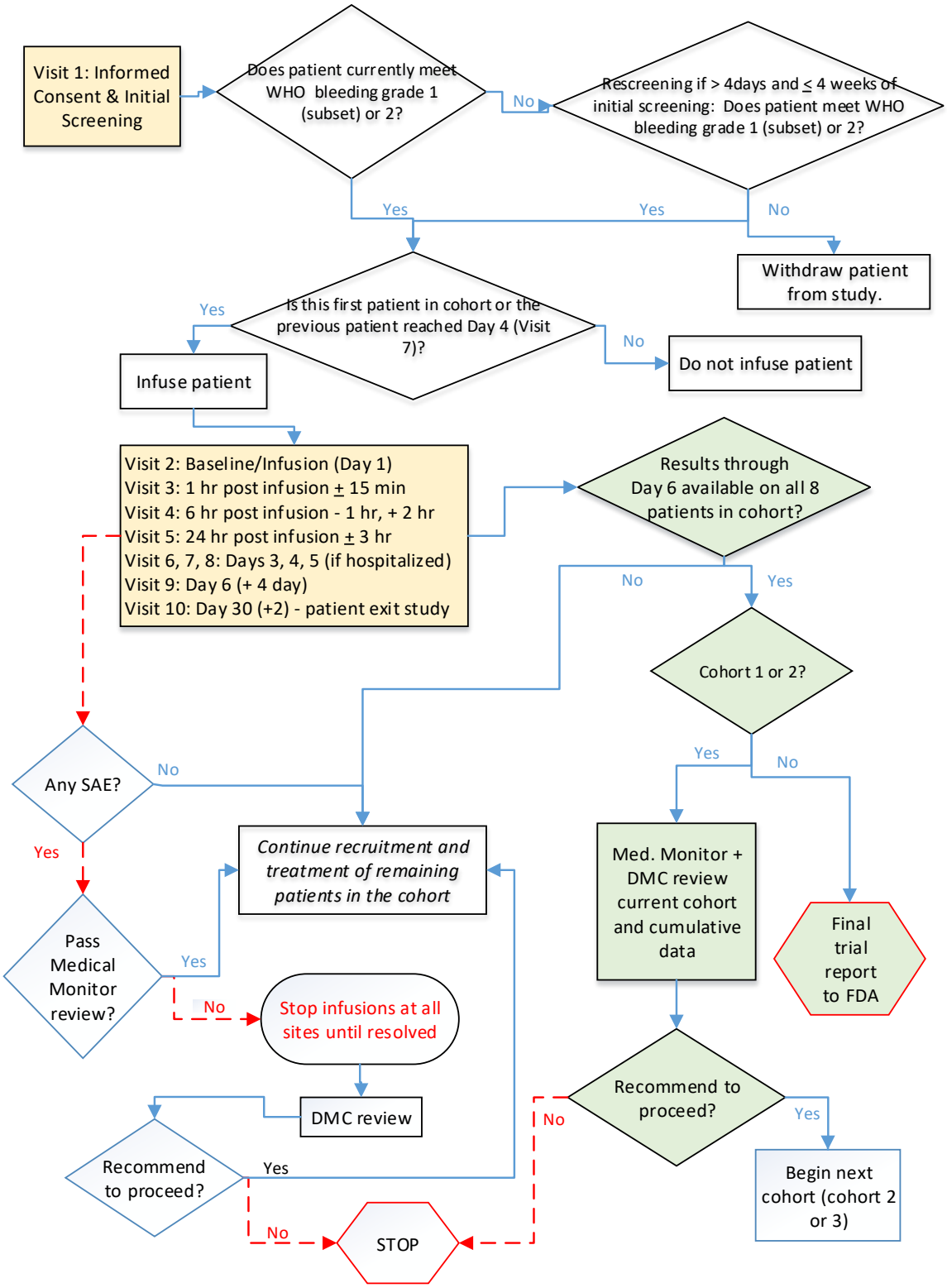
	Grade 1	Grade 2	Grade 3
			(e.g. to aspirate), and/or need for transfusion
Central Nervous System		• Retinal bleeding without visual impairment • Lumbar puncture with blood (>5 RBC/μL in CSF on microscopic analysis and non-traumatic tap), no symptoms and no visible red color	• Lumbar puncture with visible red color in absence of symptoms, and non-traumatic tap
Invasive Sites	• **Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of ≤ 1 hour in the previous 24 hours**	• Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours	• Any bleeding requiring RBC transfusion over routine transfusion needs**
Hemodynamic Instability			• Any bleeding associated with moderate hemodynamic instability (hypotension; >30mmHg fall or >30% decrease in either systolic or diastolic blood pressure) and requiring RBC transfusion over routine transfusion needs**
* Count actual bleeding (i.e. "running out" or need for basin, Kleenex, towel, etc.) not minor bleeding ** Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding			
For inclusion, Grade 1 subset bleeding includes epistaxis, hematuria, oral petechiae, oropharyngeal bleeding, or bleeding at invasive or other wound sites. See bolded items above.			

Grade 4:

- Any bleeding associated with severe hemodynamic instability (hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of > 20% for 20 minutes) and requiring RBC transfusion over routine transfusion needs
- Fatal bleeding from any source
- Retinal bleeding with visual impairment (Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consult for documentation)
- CNS symptoms with non-traumatic bloody lumbar puncture
- CNS bleeding on imaging study with or without dysfunction

Appendix B- Flow Diagram of Study Events

(Each cohort = 8 patients)



Appendix C- Definition of Myocardial Infarction

Definition of Myocardial Infarction (two or more of the following):

1. hs Troponin I or hs Troponin T level greater than the local lab reference range for normal.
2. Electrocardiograms (EKGs; at least two) showing changes from baseline or serially in ST-T and/or Q-waves that were 0.03 seconds in width and/or greater than one-third of the total QRS complex in two or more contiguous leads.

   NOTE: Other EKG findings consistent with a diagnosis of myocardial infarction may also be considered a myocardial infarction.
3. Clinical indications consistent with myocardial infarction as seen by prolonged (> 20 min) chest pain not relieved by rest and/or nitrates
4. Radiologic evidence as seen by
   A. Angiographically documented coronary artery occlusion, or
   B. Imaging evidence of loss of viable myocardium

Appendix D- Definition of ALI Adapted from NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol v2.4

ALI is defined as the presence of the following:

- NO evidence of acute lung injury (ALI) prior to infusion, and
- Radiographic evidence of bilateral infiltrates, and
- No left atrial hypertension (i.e., circulatory overload) as determined by clinical signs or left atrial pressure measurements, and
- Hypoxemia defined by any one of these methods:
  - PaO2/FiO2 less than or equal to 300 mm Hg
  - Oxygen saturation less than 90% on room air
  - Other clinical evidence

Appendix E- DVT and PE Algorithm Pages from ICSI Guideline

ICSI
Institute for Clinical Systems Improvement

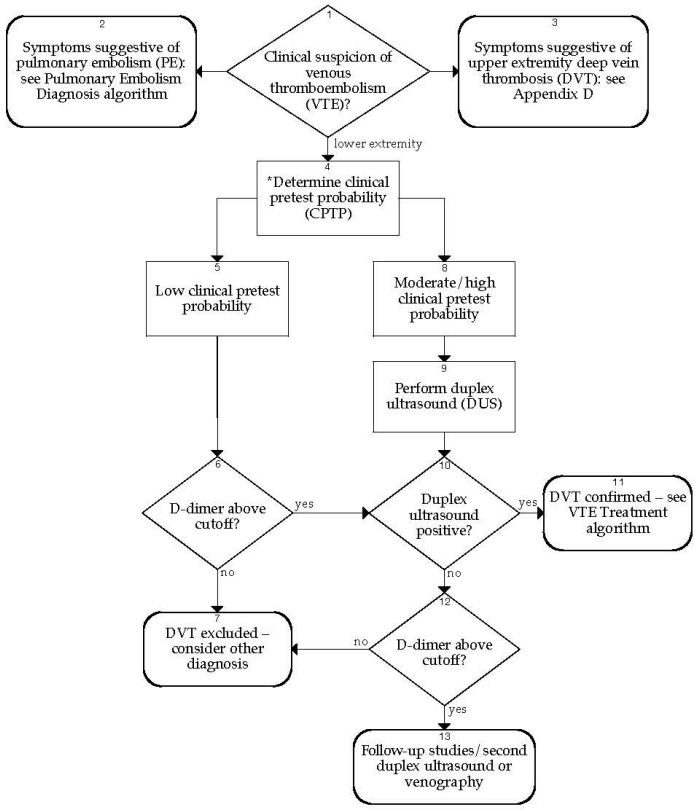
Thirteenth Edition
January 2013

Health Care Guideline:

Venous Thromboembolism Diagnosis and Treatment

Deep Vein Thrombosis (DVT) Diagnosis Algorithm

Text in blue in this algorithm indicates a linked corresponding annotation.



*4.

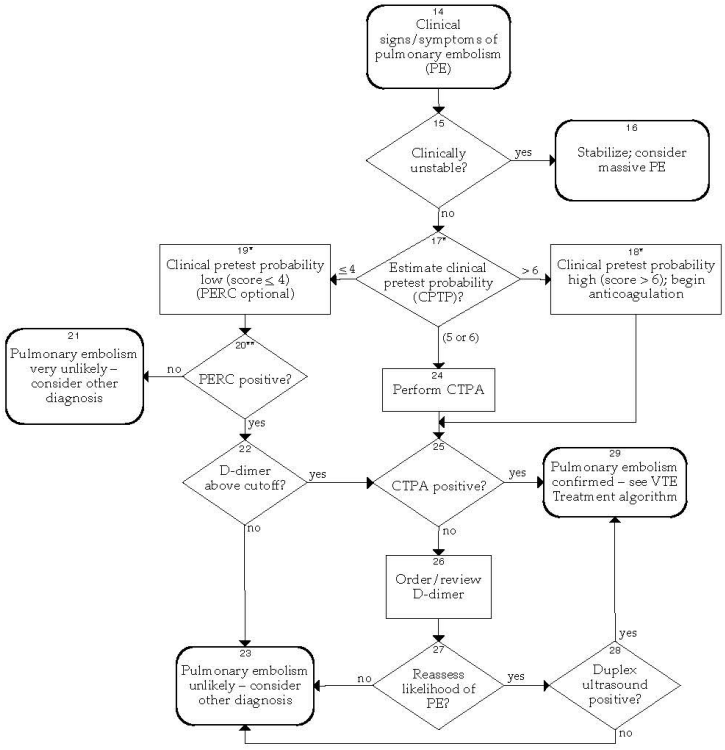
Clinical Pretest Probability (CPTP - Wells DVT Score) – See Appendix A

Active cancer (on treatment for last 6 months or palliative)	1
Paralysis, paresis or plaster immobilization of lower extremity	1
Immobilization previous 4 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swollen by more than 3 cm	1
Pitting edema	1
Collateral superficial veins (non-varicose)	1
Probable alternative diagnosis	- 2

High DVT Risk = 3+
Moderate DVT Risk = 1-2
Low DVT Risk = ≤ 0

If both legs are symptomatic, score the more severe leg.

Pulmonary Embolism (PE) Diagnosis Algorithm



*17, 18, 19

Assess Clincal Pretest Probability of Pulmonary Embolism

Clinical Pretest Probability (CPTP - modified Wells PE Score)

Clinical Signs	3
Alternative Dx unlikely	3
Heart rate > 100	1.5
Immobilization previous 4 days	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment for last 6 mo)	1

PE Less Likely ≤ 4
PE Likely > 4

Assess Pulmonary Embolism Rule-Out Criteria

**If any of these questions is answered yes, then the patient is considered PERC positive:

1. Is the patient older than 49 years?
2. Is the patient's pulse > 99 beats per minute?
3. Is the patient's pulse oximetry reading < 95% while breathing room air?
4. Does the patient have hemoptysis?
5. Is the patient on exogenous estrogen?
6. Does the patient have prior diagnosis of VTE?
7. Has the patient had surgery or trauma (requiring endotracheal intubation or hospitalization in the previous four weeks)?
8. Does the patient have unilateral leg swelling at the calves?

(*Fesmire, 2011*)

Abbreviations

CPTP = Clinical pretest probability
CTPA = CT pulmonary angiogram
PE = Pulmonary embolism
PERC = Pulmonary embolism rule-out criteria
VTE = Venous thromboembolism

Text in blue in this algorithm indicates a linked corresponding annotation.

Appendix F – Instructions for Reconstitution and Preparation of Thrombosomes for Administration

Study sites receiving, storing, preparing and administering Thrombosomes should be operating under BSL-2 workplace biosafety measures as applied in the blood establishment setting (AABB Technical Manual 19th edition chapter 2, Facilities, Work Environment and Safety). These biosafety measures address agents of moderate potential hazard to personnel and the environment, usually from contact-associated exposure to certain infectious agents. Blood banks and laboratories typically operate under these measures, and pharmacies may also designate personnel, equipment, areas and procedures for the handling of such blood products.

Appendix F.1 Supplies and Equipment Required

Investigational product is Thrombosomes. Thrombosomes are prepared from pooled human blood product and supplied for this trial as a lyophilized cake in a stoppered vial(s) for reconstitution with 10 ml sterile Water for Injection (WFI).

Supplies and Equipment for Reconstitution of Thrombosomes and Preparation of Doses

- Sterile Water for Injection, USP (may be used for multiple reconstitutions but discard at the end of the shift or day)
- Sterile 10 and 20 ml syringes
- Sterile Closed System Transfer Device (CSTD) (e.g. Chemotherapy Dispensing Pin, Universal Vial Spike with Clave or equivalent)
- Alcohol wipes
- Labels for syringe for final dose
- Sterile syringe tip cap (dual function)
- Hemo-Nate® Filter, 18 micron blood filter, (Product #402009, Utah Medical Products, Midvale, UT)

Supplies and Equipment for Administration of Dose

- IV administration set
- Syringe pump capable of delivering a 10ml to 30ml dose at 1 ml/minute

Appendix F.2 Reconstitution of Thrombosomes

Patients will require at least one vial of Thrombosomes to be reconstituted. Aseptic technique must be used in the preparation of material. Thrombosomes should be infused within one hour of reconstitution

All reconstituted Thrombosomes vial(s) should be retained at 4°C on site for at least 7 days after infusion and be destroyed at the site as a biological material after completion of the study. Unused, unopened vial(s) of Thrombosomes will be returned to Cellphire.

To rehydrate Thrombosomes:

1. Remove vial(s) from room temperature storage and visually inspect for integrity. If there are signs of breakage, damage to the seal or atypical appearance of the contents, do not use and contact Cellphire. Record on the source document the vial(s) lot number, vial number, expiration date and other information as indicated on the form. Record product information about the WFI and other supplies on the source document.
2. Carefully remove any outer packaging from the vial(s). Remove the tab of the protective cap of the vial(s) stopper, exposing the grey butyl stopper, but leaving the collar of the aluminum seal in place. Swab with an alcohol wipe
3. Swab the port on the WFI bag with an alcohol wipe [if exposed] and place a medication injection site in the port of the bag if needed. Using this site and an appropriate sterile syringe, withdraw 10 ml WFI as indicated on the vial(s) label.
4. Using a CSTD puncture the exposed stopper to allow venting of air. Keep CSTD in place.
5. Attach the syringe containing the WFI to the luerlock of the CSTD and slowly deliver the WFI to the vial(s) through the rubber stopper. Gently tip the CSTD/syringe, directing the stream against the inside side wall of the vial(s), not onto the cake. Keep CSTD and syringe in place.
6. Record the start time/date of reconstitution on the vial(s) and on the source document.
7. Gently swirl the vial(s) every few minutes until 10 minutes or the entire cake is resuspended. Rehydrated Thrombosomes should appear off-white and translucent in suspension. Note: If the product does not reconstitute within 10 minutes or demonstrates excessive clumping or discoloration upon visual inspection, do not use for transfusion and contact Cellphire. In either case an alternate vial should be selected for rehydration.
8. Thrombosomes should be transfused within one hour of the end time of reconstitution.

Appendix F.3 Preparation of Doses of Thrombosomes

A dose table will be provided with each lot in the EDC. The method used to calculate dose is shown below.

For example: Patient weight = 70 kg
Label indicates a dosage of 0.1 ml/kg body weight
70 x 0.1 =7.0 ml infusion dose.

In this example, the 7.0 ml infusion dose requires reconstitution of one 10 ml vial of Thrombosomes. If the volume calculated exceeds 10 ml, reconstitute additional number of vial(s) as required.

Once reconstitution of the Thrombosomes is complete:

9. While the CSTD/syringe in place, withdraw the volume of Thrombosomes based on the calculated dose for the patient being treated. Remove the syringe from the luerlock of CSTD.
10. Attach the sterile filter to the syringe and cover filter end with a sterile tip cap.
11. Attach syringe label with the designated recipient's ID number, product lot number, vial number and expiration (date/time) of reconstituted material and other pertinent identification information required by local procedures.
12. Provide to the responsible study personnel for infusion.
13. After infusion, place reconstituted vial(s) in 4°C storage.

Appendix G – Modified Definition of Anaphylaxis

(Supplement from Symposium on the Definition and Management of Anaphylaxis: Summary report Sampson, Hugh A. et al. Journal of Allergy and Clinical Immunology, Volume 115, Issue 3, 584 – 591 and NHSN Hemovigilance Criteria.)

Anaphylaxis is defined when any 1 of the 3 criteria are fulfilled:

1. Acute onset of an illness (up to 4 hours post-infusion) with involvement of

   Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula), and

   Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF), or

   Reduced Blood Pressure* or associated symptoms (eg, syncope)

2. Two or more of the following after exposure to known allergen for that patient (up to 4 hours post-infusion)

   History of severe allergic reaction

   Skin/mucosal tissue (eg, hives, generalized itch/flush, swollen lips/tongue/uvula)

   Airway compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF)

   Reduced BP* or associated symptoms (eg, syncope)

3. Hypotension* after exposure to known allergen for that patient (up to 4 hours post-infusion)

   *Systolic BP <100 mm Hg or >30% drop from their baseline

BP: Blood pressure PEF: peak expiratory flow.