AWARD NUMBER: W81XWH-20-1-0495

TITLE: Cold-Stored Platelets to Treat Bleeding in Cardiac Surgery Patients

PRINCIPAL INVESTIGATOR: Moritz Stolla, MD

CONTRACTING ORGANIZATION: Bloodworks Northwest

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PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Bloodworks Northwest
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Swedish Medical Center-Cherry Hill

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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14. ABSTRACT

The objective of this clinical trial is to assess the feasibility of the study protocol and preliminarily test the efficacy and safety of platelets stored at cold conditions (1-6°C) in 100% plasma for 10-14 days (CSP) in cardiac surgery patients who are actively bleeding and require platelet transfusion. The control treatment arm will receive platelets stored at room temperature (20-24°C) in 100% plasma (RSP) for up to 7 days. In this preliminary study, we are also clarifying critical mechanistic questions related to the nature of the platelet defect in the patient population under study and the post-transfusion function of stored platelets utilizing specialized laboratory assays. We hypothesize that 1) CSP are more effective than RSP at reducing blood loss and improving platelet function in subjects actively bleeding due to cardiac surgery with cardiopulmonary bypass (CPB), and that 2) CSP are safe and do not lead to increased risks relative to RSP. The overarching goal of our investigations is to evaluate the role of cold stored platelets for any actively bleeding subject with a potential platelet defect, including trauma subjects. *If our hypotheses can be supported by data, our study, together with larger follow-on studies, could have a practice-changing impact.*

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. Introduction

The objective of this clinical trial is to assess the feasibility of the study protocol and preliminarily test the efficacy and safety of platelets stored at cold conditions (1-6°C) in 100% plasma for 10-14 days (CSP) in cardiac surgery patients who are actively bleeding and require platelet transfusion. The control treatment arm will receive platelets stored at room temperature (20-24°C) in 100% plasma (RSP) for up to 7 days. In this preliminary study, we are also clarifying critical mechanistic questions related to the nature of the platelet defect in the patient population under study and the post-transfusion function of stored platelets utilizing specialized laboratory assays. We hypothesize that 1) CSP are more effective than RSP at reducing blood loss and improving platelet function in subjects actively bleeding due to cardiac surgery with cardiopulmonary bypass (CPB), and that 2) CSP are safe and do not lead to increased risks relative to RSP. The overarching goal of our investigations is to evaluate the role of cold stored platelets for any actively bleeding subject with a potential platelet defect, including trauma subjects. *If our hypotheses can be supported by data, our study, together with larger follow-on studies, could have a practice-changing impact.*

2. Keywords

Platelets, transfusion, bleeding, RSP – Room temperature stored platelets (current clinical standard control platelets), CSP – Cold stored platelets (investigational platelets)

3. Accomplishments

What were the major goals of the project?

Specific Aim 1: To assess the feasibility of the study protocol.
Specific Aim 2: To obtain data regarding the relative efficacy of CSP compared to RSP.
Specific Aim 3: To obtain data regarding the relative safety of CSP compared to RSP.

Statement of Work (updated approved version dated 30Sep2022)	**Timeline**	**Status (% completed, date)**
Major Task 1: Study Required Regulatory Approvals	Months	
Coordinate with Clinical Site for subaward agreement	1-2	Completed (not applicable)
PI will complete Investigator Agreement relevant to the entire conduct of the study at all sites.	2-3	Completed (100%, 31Mar2022)
Budgets reviewed and finalized	1-2	Completed (100%, 18May2021)
Investigational New Drug (IND) application initial approval to the U.S. Food and Drug Administration	Approval obtained 05/2019	Completed (100%, 22May2019)
IND follow-up to approval with all desired changes	1-3	Completed (100%, 15Jul2021)
Provide SMC with the Study Protocol and Informed Consent Form (ICF) template	1-2	Completed (100%, 30Jun2021)
SMC - IRB protocol submission and review	2-4	Completed (100%, Jul2021)
Funding agency HRPO review submission and review	4-5	Completed (100%, 08Oct2021) Annual renewal 23Sep2022
Submit any study protocol or ICF amendments to the IRB	As needed	Annual review approval 26Jul2022
Submit any study protocol amendments or ICF amendments to the funding agency HRPO (when appropriate)	As needed	As needed
Submit any study protocol amendments or safety updates to the FDA (for IND) as required	As needed	As needed

Coordinate with Clinical Site for annual and other required regulatory reporting (IRB, HRPO, IND)	Annually and as needed	Ongoing / As needed
Milestone Achieved: Study contract(s) signed and site budget approved	2	Completed (100%, 05Aug2021)
Milestone Achieved: IND approval	2	Completed (100%, 18May2021)
Milestone Achieved: Local IRB approval	3-4	Completed (100%, 12Aug2021)
Milestone Achieved: HRPO approval for protocol and ICF	4-5	Completed (100%, 08Oct2021)
	Timeline	**Status (% completed, date)**
Major Task 2: Process Set-Up, Development of Study Tools and Training for Implementing Study Procedures	Months	
Manufacturing implementation of per-protocol CSP manufacturing with the South Texas Blood & Tissue Center and/or Bloodworks Northwest	1-4 months	Completed (100%, 28Feb2022)
BWNW-SMC TSL staff process development and training on study platelet product ordering, receiving, processing, documenting, blinding, and issuing	2-6	Completed (100%, 28Feb2022)
Process development for documenting, ordering, and transfusing blinded study platelet products for BWNW-SMC TSL staff, SMC research personnel, and clinical staff.	2-6	Completed (100%, 28Feb2022)
Arrange for research laboratory testing sample collection, transportation, and testing	4	Completed (100%, 28Feb2022)
Research laboratory staff training as necessary for receiving samples, testing, reporting requirements and source document management	3-5	Completed (100%, Feb2022)
Develop case report forms (CRF) and electronic data capture (EDC) tools as needed to record all study measurements	3-6	Completed (100%, 12/2021)
Training for staff required to complete and verify entries on CRF and EDC system	5-6	Completed (100%, 11/2021)
Study personnel training (SMC): training for all Clinical Site research personnel and appropriate clinical staff (includes Site Initiation Visit and associated trainings)	5-6	Completed (100%, Feb2022)
Study personnel training (BWNW): training for all appropriate BWNW research staff (includes Site Initiation Visit and associated trainings)	3-6	Completed (100%, Feb2022)
Study personnel are delegated for their assigned study responsibilities by the PI	5-6	Completed (100%, Feb2022)
Milestone Achieved: Processes for study implementation are set-up and validated	5-6	Completed (100%, Mar2022)
Milestone Achieved: All study personnel are trained and appropriately delegated for their assigned responsibilities	5-6	Completed (100%, Mar2022)
	Timeline	**Status (% completed, date)**
Major Task 3: Study Enrollment	Months	Ongoing (9%, Sep 2022)
Major Task 4: Data Analysis	Months	
Major Task 5: Study Close-Out	Months	

What was accomplished under these goals?

Major Task 1: Study Required Regulatory

Approvals

All key critical items of Major Task 1 are completed.
In Year 2 there were additional IRB submissions related to a nominally updated protocol (protocol version 1.2, version1.3 and version 1.4) and the study Manual of Procedures (MOP). All items were approved by the IRB.

Major Task 2: Process Set-Up, Development of Study Tools and Training for Implementing Study Procedures

We completed significant study process development and start-up work. In October 2021, we completed the Site Initiation Visit and most related training for Swedish Medical Center – Cherry Hill. Swedish Medical Center – Cherry Hill completed start-up activities required and have begun enrollment. The Stolla Research Lab completed start-up activities and has begun processing research samples. The South Texas Blood and Tissue Center completed activation requirements and has begun processing platelet order requests.

Significant progress has been made in the development of the HLA differentiated functional assay. The functional assay has been well tested to work with five different functional markers under two different agonist, each at two different concentrations, as well as no-agonist controls. Four different HLA antibodies have been tested and calibrated to work with the functional assay, along with a pan-platelet marker. Much of the preliminary troubleshooting, workflow, and proof of concept work has been completed, and the four subjects that have been transfused have evaluable data from the still evolving exploratory assay. More work is still needed to optimize agonist concentration as well as gating strategies, as the blood form recently transfused cardiac surgery patients has characteristics that are hard to replicate using normal donors; we are optimistic that this will be achievable with more subjects in the future.

Major Task 3: Study Enrollment

Study enrollment began Year 2, Q2. Initial enrollment was slow and hampered due to significant limits placed on cardiac surgery amidst the current state of the COVID-19 pandemic. While study enrollment was initially slow, it has picked up in last 2 months and we anticipated that the study can still be completed within the initially planned timeframe.

Major Task 4: Data Analysis

Data analysis activities is not initiated until Major Task 3 is completed.

Major Task 5: Study Close-out

Study close-out is not initiated until the study database is locked after the end of subject enrollment.

Summary and Conclusion: The project team has made significant progress and has begun enrollment and we believe the clinical site team at Swedish is well equipped to implement the study in collaboration with Bloodworks. Although enrollment has been slow since starting, we anticipate an increase over the coming months. The Study Project manager and PI have met with the clinical team at Swedish Medical Center to identify possible issues with slow enrollment. Several items were identified:

- Surgery procedures were reduced in the months of May and June due to extended leave-of absence by 2 of the 4 Cardio-thoracic surgeons.
- Swedish surgery scheduling is still suffering the effects from COVID restrictions and resulting decreased workforce. Surgical cases are often postponed or cancelled.
- It was noted that half of the eligible subjects did not have a pre-op appointment scheduled in the study time-window. This item was addressed by submission/approval of a modification to the IRB allowing for remote consenting.
- As of 30Sep2022 11 subjects had been consented and enrolled but only 4 received platelets during the treatment window. This may reflect a decrease in platelet use by the cardio-thoracic team or simply be a result of less subjects who are eligible.

Regulatory Protocol and Activity Status

PROTOCOL (1 of 1 total):

Protocol Number: 2021-01

HRPO Log Numbers: E01348.1a (Bloodworks Northwest Research Institute) and E01348.1b (Swedish Medical Center-Cherry Hill)

Title: Evaluation of Efficacy and Safety of Extended Cold Stored Apheresis Platelets versus Conventional Apheresis Platelets in Cardiac Surgery Patients (CHASE Trial)

Target evaluable subjects required for statistical significance: Unspecified in statistical plan (primary endpoint is feasibility)

Target approved: 30 evaluable subjects (up to 100 enrolled).

Submitted to and approved by:

FDA – IND #18981

- Initial submission: 08Apr2019
  - Approval: 22May2019
- Annual report submission (2020): 21Jul2020
- Ind protocol modification submission: 07May2021
  - Approval: 15Jul2021
- Annual report submission (2021): 09Jul2021
- FDA form 1572 modification submission: 24Sep2021
- Ind protocol modification submission: 04Jan2022
  - Approval 17Feb2022
- Annual report submission (2022): 18Jul2022

IRB – Providence St. Joseph IRB (PSJ-IRB)

- Initial submission: 02Jul2021--Approval: 12Aug2021
- Modification #1 Approval 24Nov2021
- Modification #2 Approval 10Dec2021
- Modification #3 Approval 25Jan2022
- Modification #4 Approval 01Mar2022
- Modification #5 Approval 08Aug2022
- Modification #6 Submitted 26Sep2022, approval pending

- Annual Review Approval 26Jul2022

HRPO [HRPO Log Numbers: E01348.1a (Bloodworks Northwest Research Institute) and E01348.1b (Swedish Medical Center-Cherry Hill)]

- Initial submission: 17Aug2021-- approval: 08Oct2021
- Annual Review: approval 27Sep2022

STATUS: Y2 (2021-2022)

(i) Number of subjects recruited/original planned target: 9/38
Number of subjects screened/original planned target: 25/no screening target in SOW
Number of patients enrolled/original planned target: 9/38
Number of patients completed/original planned target: 9/38

Protocol Number	**Protocol PI Name**	**Organization (Site)**	**# Target**	**# Enrolled**	**# Completed**	**# Evaluable (received platelets during the study window)**
2021-01	Moritz Stolla, MD	E01348.1b (SwedishMedical Center-Cherry Hill)				
		This reporting period	7	5	5	3
		Cumulative	38	9	9	4

Protocol Number	**Protocol PI Name**	**Organization (Site)**	**# Target**	**# Enrolled**	**# Completed**	**# Evaluable (received platelets during the study window)**
2021-01	Moritz Stolla, MD	E01348.1a (Bloodworks NW)				
		This reporting period	0	0	0	0
		Cumulative	0	0	0	0

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting year (Q4 2022-Q3 2023), we have the following goals broken down by reporting quarter.
Q4 2022: We aim to continue study enrollment and subject accrual during the quarter with targeted enrollment of at least 6 subjects per month. Additionally, we anticipate finalizing development of the HLA exploratory functional assay.
Q1 2023: We aim to continue study enrollment and subject accrual during the quarter with targeted enrollment of at least 6 subjects per month. We tentatively aim to submit a methods manuscript describing the developed HLA exploratory functional assay in Q1 2023 or Q2 2023.
Q2 2023: We aim to continue study enrollment and subject accrual during the quarter with targeted enrollment of at least 6 subjects per month.
Q3 2023: We aim to continue study enrollment and subject accrual during the quarter with targeted enrollment of at least 6 subjects per month.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report.

What was the impact on other disciplines?
Nothing to Report.

What was the impact on technology transfer?
Nothing to Report.

What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
The protocol was amended in September 2022 reducing the research blood sampling from 27 ml to 10 ml for each of the 4 timepoints. We eliminated the Whole Blood Aggregometery testing and will use the clinically available coagulation and CBC results. This change occurred following hesitancy of the SMC Cardiothoracic to draw research blood samples prior to transfusion of platelets (baseline labs).

Actual or anticipated problems or delays and actions or plans to resolve them

Initiation of enrollment was delayed for several reasons previously discussed in the 2020-2021 Annual report.

The project team has made significant progress and has begun enrollment and we believe the clinical site team at Swedish is well equipped to implement the study in collaboration with Bloodworks. Although enrollment has been slow since starting, we anticipate an increase over the coming months. The Study Project manager and PI have met with the clinical team at Swedish Medical Center to identify possible issues with slow enrollment. Several items were identified:

- Surgery procedures were reduced in the months of May and June due to extended leave-

of absence by 2 of the 4 Cardio-thoracic surgeons.

- Swedish surgery scheduling is still suffering the effects from COVID restrictions and resulting decreased workforce. Surgical cases are often postponed or cancelled.
- It was noted that half of the eligible subjects did not have a pre-op appointment scheduled in the study time-window. This item was addressed by submission/approval of a modification to the IRB allowing for remote consenting.
- As of 30Sep2022 11 subjects had been consented and enrolled but only 4 received platelets during the treatment window. This may reflect a decrease in platelet use by the cardio-thoracic team or simply be a result of less subjects who are eligible.

As subjects are enrolled, we continue to adjust the exploratory assay (HLA discriminating functional assessment of transfused platelets flow cytometry assay).

We have experienced issues with failure on visual inspection due to aggregates in the storage bags in 9 of the 16 Cold Stored Platelets (CSP) shipped to the clinical site. The units not passing visual inspection were not used. We have discussed this issue with the CSP supplier and are working on a possible solution.

Anticipated Problems/Issues

Even though Swedish Medical Center – Cherry Hill is open for enrollment it is apparent that early enrollment is limited as cardiac surgeries are catching up with previous holds related to limitations caused by restrictions of the COVID-19 pandemic. The magnitude and duration of the impact on recruitment is difficult to forecast and every effort will be made to maximize opportunities to recruit/enroll patients when appropriate patients are scheduled for surgery.

Changes that had a significant impact on expenditures

Costs were lower than anticipated because enrollment did not occur in until Q1 2022. We anticipate increased costs in future reporting periods where such enrollment associated costs will be increased.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Nothing to Report.

Journal publications

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

- **Website(s) or other Internet site(s)**

  Nothing to Report.

- **Technologies or techniques**

  Nothing to Report.

- **Inventions, patent applications, and/or licenses**

  Nothing to Report.

- **Other Products**

  Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Moritz Stolla, MD
No change

Name: Jeffrey A Miles, BA, MS
No longer working on this project.

Name: Patricia Klotz, BSN
No change

Name: Shawn Bailey, BS
No change

Name: Jennifer Nagel, BS
No change

Name: Inger Rasmussen, BA
No change

Name: Caroline Petgrave, BA
No change

Name: Andrea Drouhard, BA
No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?
Organization Name: Swedish Medical Center – Cherry Hill
Location of Organization: 500 17th Avenue, Seattle, WA, 98122
Partner's contribution to the project: collaboration
Description: Swedish Medical Center – Cherry Hill is the clinical site for this project's only clinical study protocol and they are a subawardee of this project. Their research staff completes site Research Coordinator and other related site research activities.

Organization Name: South Texas Blood and Tissue Center
Location of Organization: 6211 I-10, San Antonio, TX 78201
Partner's contribution to the project: Other
Description: The South Texas Blood & Tissue Center provides a licensed CSP product for use as an investigational product in the CHASE Trial.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

The Quad Chart has been appropriately included as indicated.

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

The following historical patient procedure type data is reproduced from email correspondence received by Bloodworks Northwest from Bob Fletcher at Swedish Medical Center – Cherry Hill on March 23, 2021:

Updated Clinical Site (Swedish Medical Center – Cherry Hill) Procedure Volume

Surgery Type	2017	2018	2019	2020	Annual Avg
Re-do surgeries	36	45	28	37	36.5
Triple valve	9	9	6	0	6
Complex aortic surgery	59	66	61	38	56
All	104	120	95	75	98.5*

*Adjusting for cases falling in multiple categories (i.e., unique patients): 83 per year