

AWARD NUMBER: W81XWH-20-1-0652

TITLE: *Can Preoperative Skin Perfusion Predict Wound Healing Complications in High-Risk Peri-Articular Tibial Fracture Fixation*

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CONTRACTING ORGANIZATION: University of Maryland, Baltimore

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
This prospective single group observational study will enroll 160 patients with closed peri-articular tibial fractures that require surgical fixation from three trauma centers in the United States. Following informed consent, eligible patients will undergo LA-ICGA perfusion measurements of their injured limb at their index surgery as well as their delayed open definitive surgery (if required). The perfusion will be standardized relative to the capillary ICG concentration as measured by a pulse dye densitometer. Patients will be assessed at regular clinical follow-up visits for 90 days after definitive fixation and monitored for the primary outcome of wound complications.

15. SUBJECT TERMS

NONE LISTED

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1. INTRODUCTION:

Using a commercially available LA-ICGA system to objectively measure soft-tissue perfusion, our proposed research continues the work from our pilot studies. The current study will establish the relationship between preoperative soft tissue perfusion and postoperative wound complications for periarticular tibia fractures. Additionally, the study will quantify the magnitude of perfusion recovery from the time of injury to definitive fixation when a delayed fixation strategy is selected.

2. KEYWORDS:

- **IRB** – Internal Review Board
- **HRPO** – Human Research Protections Office
- **DoD** – United states Department of Defense
- **UMD** – University of Maryland, Baltimore
- **DHMC** – Dartmouth-Hitchcock Medical Center
- **UCI** – University of California, Irvine Medical Center
- **LA-ICGA** – Laser Assisted Iodocyanine Green Angiography
- **SPA** – Sponsored Programs Administration
- **SPAC** – Sponsored Programs Accounting & Compliance

3. ACCOMPLISHMENTS:

What were the major goals of the project?

- Draft, edit and submit protocol to University of Maryland, Baltimore IRB
- Submit protocol to HRPO
- Draft, modify and finalize case report forms (CRFs) for enrollment and follow-ups
- Build digital database for CRFs using UMD's REDCap
- Establish subcontracts between UMD, Dartmouth-Hitchcock Medical Center, and University of California Irvine
- Site Training and Professional Development
- Enrollment: 160 patients (across all sites; 120 UMB and ~40 DHMC/UCI)
- Achieve 100% primary outcomes at all patient follow-up timepoints
- Perform site monitoring and data validation
- Data collection, cleaning, validation, and analysis (all sites)
- Manuscript preparation and other knowledge translation activities

What was accomplished under these goals?

Summary CY3 (Q1-Q3):

- UMD continued subject recruitment, enrollment, and LA-ICGA data collection during Q1-Q3. Out of 105 patients screened; 68 were ineligible, 11 **missed***, 9 refused and 18 consented / enrolled in the study. Overall enrollment during this period was 42 participants.

**Missed patients are defined as individuals that were deemed eligible but were not approached for consent prior to surgery because it occurred outside business hours, on weekend / holiday or occurred concurrently with another procedure. In Q3, UMD presented its enrollment projections and plans to the study's Scientific Officer. Essentially, participants would be consented on weekends and after hours in an effort to increase enrollment. Refer to "Enrollment Projections" in the Appendices (page 12) for details.*

- During Q1-Q3, LA-ICGA perfusion measurements were collected on 18 subjects; 7 at definitive fixation only, 1 ex-fix only, and 10 at index (ex-fix) surgery + delayed open definitive fixations.
- Follow-ups; 12 subjects were in active follow-up and 30 completed follow-up during this period. Primary outcomes remained ~96%, 96% and 95% at the 2-week, 6-week and 3-month patient follow-up timepoints, respectively. No adverse events, complications, surgical site infections, unplanned surgeries or rehospitalizations were reported during follow-up clinic visits.

Summary CY3 (Q1-Q3 cont'd):

- Continuing Review #2 was approved by local IRB with expiration date of 12/21/2023. Relying sites were updated with necessary approval letters and newly date-stamped informed consent documents. Additionally, UMD IRB approved the informed consent form for remote LAR consenting.
- DHMC continued site start up procedures; team access to UMB's RedCap database. Renewal of DHMC's reliance agreement was approved and submitted to SPA.
- UCI's informed consent document received local IRB approval. Additionally, UCI amended their subaward contract to adjust for ICG dye costing. The amended contract was resubmitted to SPAC and pending revision and approvals.

CY3 Q4:

- Participant screening, enrollment, ICG data collection and follow-up activities continued at UMD during part of the CY3 Q4. A total of 39 patients were screened; 6 deemed ineligible, 31 missed (due to device malfunction, see below*), 0 refused and 2 consented to the study. Current overall enrollment is 44 out of 120 subjects. DHMC and UCI have not initiated enrollment activities at this time.

** On August 1, 2023, the SPY Elite machine malfunctioned during LA-ICGA data collection. The machine has reached End of Service Life per the vendor, Stryker. UMD's Clinical Engineering Team diagnosed the touchscreen as faulty and an internal error with hard drive processing. As a result of the machine being out of service, all enrollment and intraoperative LA-ICGA data collection activities have been paused. However, participant screening and clinic follow-up activities continued through end of Q4.*

- LA-ICGA perfusion measurements were collected on 2 subjects during definitive fixation.
- Currently, 1 subject is in active follow-up and 43 completed follow-up at the 3-month timepoint. Primary outcomes are 98%, 95% and 100% at the 2-week, 6-week and 3-month patient follow-up timepoints, respectively. No subjects reported adverse events, complications, surgical site infections, unplanned surgeries or rehospitalizations.

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

- UMD recruited and trained 3 new team members during CY3 Q3. All new team members obtained CITI Group 1 and 2 certifications and are proficient in screening, consent, enrollment, and LA-ICGA perfusion data collection / analysis, per the study protocol.
- UMD conducted refresher training for Research Staff and Interns in Q3 to better streamline consenting, enrollment, and follow-up activities.
- DHMC initiated site training for its new team members in Q2 & Q3. Training activities will continue prior to patient enrollment.

How were the results disseminated to communities of interest?

- Data collection at UMD is currently in process. Preliminary results from day-to-day activities are only discussed amongst the Study Team on a weekly basis to address challenges, concerns and accomplishments. It is anticipated that once the study reaches data analysis phase, results will be disseminated to communities of interest.

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

- By the next reporting time-point we expect:
- By the next reporting timepoint we expect:
 - UMD will continue to screening and follow-up activities, and resume subject recruitment and LA-ICGA intraop data collection at the local site.
 - UMD will resolve / acquire a SPY machine to resume recruitment and data collection activities. It is anticipated the SPY PHI trial will be successful and local site will acquire the device.
 - UCI’s subaward contract will be finalized and approved.
 - DHMC Teams will have access to the MD REDCap database and initiate enrollment activities.
 - UMD will add UCI Team to local IRB and provide MD REDCap Access.
 - UMD will remain in regular contact with participating sites to ensure these goals are accomplished in a timely and efficient manner and provide guidance to resolve challenges with site start-up.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

- It is anticipated this study will meet over 95% primary outcomes at all clinic follow-up timepoints. As such, LA-ICGA may be useful in predicting post-operative wound complications.

What was the impact on other disciplines?

- To be determined once data collection and analysis is complete from all sites.

What was the impact on technology transfer?

- To be determined once this phase of the study is completed.

What was the impact on society beyond science and technology?

- It is anticipated that this study will determine if LA-ICGA is useful prognostic tool that surgeons can use to objectively guide their surgical decision making, specifically relating to the use of delayed fixation and optimal timing of definitive open fixation. The overarching goal is to minimize infection while safely expediting patient recovery and rehabilitation.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

- At this time, no changes in approach were deemed necessary.

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

- The SPY Elite machine malfunction was a major delay and set-back in enrollment in Q3. UMD is working with Stryker to trial test the next generation imager, SPY PHI, which a portable handheld device at no cost. Once the trial terms and conditions are finalized, UM will test device to ensure data is comparable across devices (Elite vs PHI).

Changes that had a significant impact on expenditures

- No significant changes were made to impact expenditures.

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

- No changes 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:	Dr. Raymond Pency
Project Role:	Principal Investigator, UMD (Lead Site Protocol Chair)
Months Worked:	32
Contribution to Project:	Dr. Pency provides overall project leadership and oversight.
Funding Support:	n/a

Name:	Dr. Gerard Slobogean
Project Role:	Co-Investigator, UMD
Months Worked:	32
Contribution to Project:	Dr. Slobogean provides on-going scientific and medical oversight.
Funding Support:	n/a

Name:	LaShann Selby, MS, MPH
Project Role:	Clinical Research Coordinator, UMD (Lead Site POC)
Months Worked:	19
Contribution to Project:	Ms. Selby provides daily project oversight and management of study implementation (patient screening, enrollment, follow-up visits and data collection efforts). Maintains study documentation, case report forms, IRB applications and continuing reviews at lead site. Ms. Selby will provide site monitoring and data quality control to participating sites (UCI & DHMC).
Funding Support:	n/a

Name:	Heather Phipps, MPS
Project Role:	Clinical Research Specialist, UMD
Months Worked:	21
Contribution to Project:	Mrs. Phipps provided oversight on project start-up at the lead and participating sites, as well as IRB/HRPO and other regulatory matters at UMD.
Funding Support:	n/a

Name:	Alice Bell
Project Role:	Research Intern, UMD
Months Worked:	4 (CY3Q3 - present)
Contribution to Project:	Ms. Bell participates in patient screening, enrollment, LA-ICGA data collection and patient follow-ups.
Funding Support:	n/a

Name:	Vivian Li
Project Role:	Research Intern, UMD
Months Worked:	3.5 (CY3Q3 - present)
Contribution to Project:	Ms. Li participates in patient screening, enrollment, LA-ICGA data collection and patient follow-ups.
Funding Support:	n/a

Name:	Murali Kovvur
Project Role:	Research Intern, UMD
Months Worked:	10 (CY2Q3 – CY3Q3)
Contribution to Project:	Mr. Kovvur participated in patient screening, enrollment, LA-ICGA data collection and patient follow-ups.
Funding Support:	n/a

Name:	Joshua Lawrence
Project Role:	Research Intern, UMD
Months Worked:	11 (CY2Q3 – CY3Q3)
Contribution to Project:	Mr. Lawrence participated in patient screening, enrollment, LA-ICGA data collection and patient follow-ups.
Funding Support:	n/a

Name:	Kristin Turner
Project Role:	Research Intern, UMD
Months Worked:	11 (CY2Q3 – CY3Q3)
Contribution to Project:	Ms. Turner participated in patient screening, enrollment, LA-ICGA data collection and patient follow-ups.
Funding Support:	n/a

Name:	Kathleen Healey
Project Role:	Research Intern, UMD
Months Worked:	13 (CY2Q1 - CY3Q1)
Contribution to Project:	Ms. Healey participated in patient screening, enrollment, LA-ICGA data collection and patient follow-ups.
Funding Support:	n/a

Name:	Dr. Leah Ida Gitajn
Project Role:	Co-Investigator, DHMC
Months Worked:	n/a
Contribution to Project:	No change to report. Dr. Gitajn is prepared to contribute to the study once the subcontract is finalized and site training has been completed.
Funding Support:	n/a

Name:	Dr. John Scolaro
Project Role:	Co-Investigator, UCI
Months Worked:	n/a
Contribution to Project:	No change to report. Dr. Scolaro is prepared to contribute to the study once the subcontracts, reliance agreements, and IRB/HRPO approvals are in order
Funding Support:	n/a

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

- No changes in support of PI or other senior/key personnel were made during this contract year.

What other organizations were involved as partners?

- DHMC and UCI have agreed to support the project by enrolling and following 40 participants. DHMC has received UMD and local site IRB approvals to begin study procedures. UCI must seek local IRB approval of their informed consent document prior to initiating study procedures.
 - **Organization Name:** (1) University of California at Irvine Medical Center; (2) Dartmouth-Hitchcock Medical Center
 - **Location of Organization:** (1) Orange, California; (2) Lebanon, New Hampshire
 - **Partner's contribution to the project**
 - **Collaboration-** Partner sites are expected to contribute to this project in the near term. It is highly anticipated that DHMC will initiate their processes in CY24 Q1, and UCI thereafter.

8. SPECIAL REPORTING REQUIREMENTS

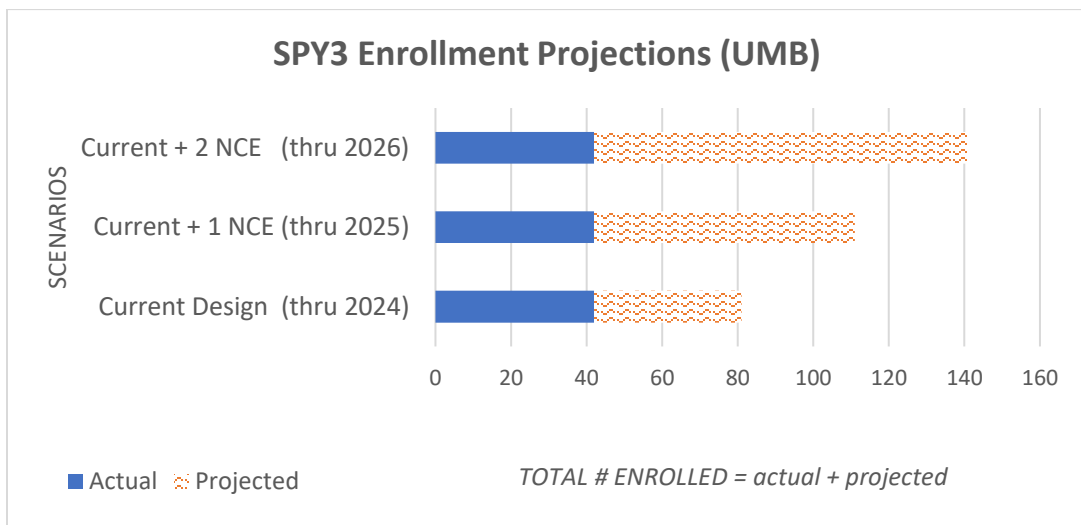
COLLABORATIVE AWARDS: Nothing to Report.

QUAD CHART: Updated to reflect CY 20 – CY23 Q4. Submitted as a separate document

9. APPENDICES

Enrollment Projections:

- UMD devised the following 3 scenarios to guide our enrollment projection to 120 participants by the end of the contract term (September 2024). Details of the scenarios are summarized below and in the bar chart. These projections are based on the following assumptions;
 - Enroll ≥ 3 participants per month, 7 days/week (including weekends and holidays); It was determined that a substantial portion of patients were “missed” because surgeries occurred outside business hours, on weekends or holidays. Moving forward, UMD will enroll patients on weekends/holidays and beyond business hours as necessary.
 - November and December expect low / no enrollments.



Scenario 1: Current Design (Thru 2024)

- Starting at baseline of 42 (actual enrolled to date in “blue”). Enrolling at least 3 patients/month the projected enrolled thru September 2024 is 39 (orange). Total enrolled (actual + projected) = 81. In this scenario, we meet our goal of 120 total enrolled by 68%.

Scenario 2: Current Design + 1 No Cost Extension (NCE) Thru 2025

- Starting at baseline of 42 (current enrolled “blue”). Assuming at least 3 patients are enrolled/month thru September 2025, the projected enrolled is 69 (orange). Total enrolled = 111. Therefore, we meet our goal of 120 total enrolled by 93%.

Scenario 3: Current Design + 2 NCE (Thru 2026)

- Starting at baseline of 42, if at least 3 patients/month are enrolled thru September 2026, the projected enrolled is 99 (orange). Thus, total enrolled = 140. Here, we exceed our goal by 20 patients.