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TITLE: Near Infra-Red Spectroscopy to Reduce the Phrophylactic fasciotomies for and Missed Cases of Acute Compartment syndrome in Solders Injured in OEF/OIF

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14. ABSTRACT The NIRS research project is a three-part project originally planned to be completed over three years to validate the accuracy and reliability of a specific NIRS sensor (Equanox, Nonin, Inc, Plymouth, MN) in diagnosing acute compartment syndrome in injured combat soldiers. Part 1 is a series of two observational studies, the first of which was completed in Period 1. Patient will receive continuous NIRS and vital sign monitoring throughout their standard course of care, first at Landstuhl Regional Medical Center and then at 3 civilian trauma centers in Georgia. The civilian observational study is currently under IRB review and will be conducted under abbreviated FDA IDE requirements. Part 2 involves animal studies aimed at addressing issues raised in clinical testing and furthering the understanding of NIRS response to compartment syndrome. This phase of study occurred over Period 2 under IACUC and ACURO approved protocols. The final part of this project will be the translation of the current technology into a validated, FDA approved format. This requires the data collected in Parts 1 and 2, as well as ongoing regulatory steps and ultimately an investigational trial that we plan to conduct following the completion of DR080018.					
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Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	5
Key Research Accomplishments.....	9
Reportable Outcomes.....	10
Conclusion.....	11
References.....	11
Appendix	12

INTRODUCTION:

The NIRS research project is a three-part project which was planned to be conducted over three years to validate the accuracy and reliability of a specific NIRS sensor (Equanox 7600 Oximeter, Nonin, Inc, Plymouth, MN) in diagnosing acute compartment syndrome in injured combat soldiers and civilians with high-energy trauma. Part 1 (Tasks 1-2) was to be a series of two observational studies, which would enroll 135 patients in the first study (Phase 1) and 120 patients in the 2nd study (Phase 2). Patients would receive continuous NIRS and vital sign monitoring throughout their standard course of care, first at Landstuhl Regional Medical Center (Phase 1 – Completed in Period 1) and then at 3 civilian trauma centers in Georgia (Phase 2 – At IRB/USAMMDA-FDA review). This part has been initiated and Phase 1 is complete. While Phase 2 was supposed to be conducted over the course of Period 2, this observational study was severely delayed secondary to the MRMC IRB approval process, which ultimately required a protocol that was resourced and IRB-approval ready in August 2010, to be transitioned from a waived-consent protocol to an FDA regulated clinical study with required consent. This transition ultimately led to the termination of the study as originally proposed. At the onset of the study, we planned and coordinated to conduct the Phase 2 study in-theater (at Level III CSHs in Afghanistan and Iraq). While we had procured commander and logistical support, to include commitment from the JC2RT and deploying a research resident to initiate and conduct the initial part of this trial, a series of decisions by the USAMRMC IRB led to an ultimate determination that this study could NOT be performed in the combat setting. This final determination was not made until 25 Feb 2011. Since then we have worked tirelessly to find a way forward to accomplish this vital military relevant research. These efforts are outlined in the “updated overview” section of the Revised SOW (Appendix 1) which was approved on July 7, 2011, as part of the transfer of our award from the T.R.U.E. Research Foundation to The Geneva Foundation, a transfer that was brought on by the abrupt insolvency of T.R.U.E. which occurred in April 2011.

Part 2 (Task 3) involves animal studies aimed at addressing issues raised in clinical testing and furthering the understanding of NIRS response to compartment syndrome. While preparatory work began at the end of Period 1, this phase of study occurred in Period 2 under IACUC and ACURO approved protocols (University of Georgia IACUC – Protocol #: A2010 1-012). All animal studies are complete at this time (Completed 27 May 2011). Data analysis, interpretation and presentation in the form of podium, poster and manuscript is on-going.

The final part of this project (Tasks 4-6) will be the translation of the current technology into a proven, FDA approved format. This requires the data collected in Parts 1 and 2, as well as ongoing regulatory steps, iterative maturation of the diagnostic algorithm and ultimately an investigational trial we plan to conduct at the conclusion of this research project. The current FDA approved indication for the Nonin Equanox Oximeter is for “monitoring” regional tissue oxygenation. The distinction between this indication and a subsequent indication which we seek to develop, submit and defend using the results of the clinical and animal research completed in support of this grant and the investigational study to follow, is that we seek to add a “diagnostic” indication, such the device will be to be approved to provide information that directly impacts clinical decision making, which is a function that will fill the critical unmet need in combat casualty care we originally identified in our grant proposal.

BODY:

The primary goal of work conducted in Period 2 was to analyze/publish/present data from Phase 1 and complete Phase 2 along with the Task 3 animal studies.

To date, we have completed Phase 1. Our original Phase 2 Protocol was submitted to the Joint Combat Casualty Research Team (JC2RT) team on 25 Mar 2010 to begin what became an 11-month review process that ultimately ended with a final disapproval notice on 25 Feb 2011. Over the last 3 months of the review process and the 6 months since, we have arduously sought to find a new way forward. We presented a viable alternative course of action plan to USAMRAA (Drs. Taliaferro, Hack and Vandrey) in Spring 2011. With USAMRAA approval, we will successfully transition the Phase 2 study from the deployed combat setting of Afghanistan with 100% "free" labor (in the form of deployed military researchers), to 3 civilian trauma centers in Georgia, with completely grant-funded personnel support for the research activities which will be conducted as an FDA IDE trial. As this is a very significant change in plan, we have kept our USAMRAA GOR fully briefed on the status of this transition plan. To formalize this transition we received approval to transfer our award to The Geneva Foundation on July 7, 2011 with a new approved budget and SOW through the end of Period 3, and on 26 September 2011 we submitted a modification request to extend the grant by 1 additional year to make up for time lost over Period 2 as a result of the inability to proceed with the Phase 2 study as originally planned. We have requested additional funds for this extension. We have verbally presented this plan to USAMRAA and received positive feedback. We look forward to receiving formal approval for the 4th year and budget extension in the coming month. This will mark the full transition from a military to civilian setting, a process that will salvage needed success from what appeared to be a terminal setback.

The following tasks from our current statement of work were addressed over the last year:

TASK 1. Human Use Study Phase 1

1a-d. Completed on time in Period 1.

1e. Complete Phase 1 Prospective Observational Study. Completed

1f. Analyze Data, Provider Feedback and Amend Phase 2 Methodology as needed – Completed. We have completed all data analysis for Phase 1.

1g. Present/Publish Results of Phase 1 – Ongoing - We have presented abstracts in podium and poster presentation at 4 meetings this year (AAOS, ATACC, EWI (METRC steering commitment and break-out session), SOMOS) and are prepared to submit the manuscript for publication. (See Reportable Outcomes section for further details) (Appendix 2)

TASK 2. Human Use Study Phase 2

2a. Create and Submit Human Use IRB Protocol Application: Ongoing (due 1 Oct 2010) – We have modified this part of the grant substantially in response to 3 primary problems: (1) rejection of our original Phase 2 IRB protocol by MPMC and the need to perform this study under FDA IDE abbreviated requirements, (2) sale of Somanetics, Inc to Covidien, Inc. producing a need to find a new NIRS COTS provider (Nonin, Inc. the NIRS COTS provider for the METRC Acute Compartment Syndrome Study, a synergistic DoD/USAMRAA funded ACS study) and (3) bankruptcy of TRUE Research Foundation. On 28 Mar 2011, Drs. Shuler, Taliaferro and Freedman had a TELCON to present the details of our proposed SOW and budget modifications to respond to the 3 problems outlined above. The goal was to develop a modification that would allow our project to proceed successfully. The conclusion of this discussion was that the plan was sound and the ~10% increase in overall budget to cover the additional costs related to civilianizing the study and adding an additional year to make up for the year lost in the IRB process for our original Phase 2 protocol was

reasonable. We answered Dr. Taliaferro's questions in response to our TELCON and on 8 April 2011, we submitted by email a revised SOW and Budget. On 19 April 2011, we had a 2nd TELCON with Dr. Taliaferro. This included Drs. Hack and Vandre as well. Again, the modification plan was presented and endorsed unofficially. We have worked to finalize the modification since then, but this process has had to run in tandem with the transfer of our grant award from the now defunct TRUE Foundation to The Geneva Foundation.

While we were working with USAMRAA/CDMRP to modify our grant, the T.R.U.E. Research Foundation was in the process of declaring itself to be defunct. During this quarter, we were guided through the bankruptcy process by Ms Kathryn Dunn of USAMRAA. We identified another recommended non-profit grant managing foundation, which services other DoD funded grants at LPMC—The Geneva Foundation. We have worked with our POC at the Geneva Foundation, Angela Silva, to officially transfer our grant to them. A modification was issued to award the grant to The Geneva Foundation. The modification was effective as of 7 July 2011.

The impact of this series of setbacks and hurdles on task 2a is that we have made repeated revisions to the Phase 2 protocol in the templates for all three local IRBs (Grady, Atlanta Medical and Athens Regional), but we have not yet been able to submit them for review. We are within 1-2 weeks of including all changes needed to satisfy FDA requirements. To accomplish this task, we have worked closely with USAMMDA (the FDA "sponsor" for this study, Ms Marieann Brill is our primary POC), MPMC and the Decision Gate office to leverage their experience and expertise to navigate through this challenging process. The conversion to a FDA compliant protocol, has required multiple, iterative changes, each with its own set of challenges. For example, the Phase 1 study database was maintained on MS Access, however this software is not FDA compliant for reporting, auditing and data cleaning. Thus, we have had to seek alternative options, with the final being bidding the data collection plan to a CRO. While these challenges have each led to small delays, the delays have been additive and we still are yet to be cleared to submit our protocols to the local IRBs for review. We have briefed the local IRBs and they are well aware of our protocols and the fact that the methodology and data collection/analysis plans have been thoroughly reviewed and vetted over the last 15 months. We expected immediate approval from each site. We have also pre-notified AHRPO, our 2nd level reviewer for this study, and they too stand ready to provide expeditious approval. We expect to complete this process in the coming 4-6 weeks.

2b. Obtain clearance and impact statements – Completed

2c. Recruit lead investigator for Grady, Atlanta and Athens Regional Medical Centers - Completed

2d. Conduct Phase 2 Prospective Observational Study – (Pending) We will initiate the Phase 2 study promptly after receiving local IRB approval from each study site and second level approval from AHRPO.

2e. Analyze Data, Provider Feedback -(Pending – not due until Period 3)

2f. Present/Publish Results of Phase 2- (Pending – not due until Period 3)

TASK 3. Animal Use Study – We plan to start animal studies in Oct 2010 at UGA

3a. Create and Submit UGA IACUC Protocol Application – Completed

3b Obtain approval from UGA IACUC and USAMPMC ACURO - Completed

3c. Initiate Animal Studies outlined under Aim 2. Completed -First studies initiated 15 Dec 2010,

3d. Conduct Animal Studies outlined under Aim 2. Completed – Animal studies at the University of Georgia were completed on 27 May 2011.

TASK 4. Reduction to Practice and FDA Approval Process

4a. Finalize product development relationships between Nonin, Inc and J+M Shuler (Completed) – In 4th quarter of Period 1, Somanetics, Inc. (our original vendor for our COTS NIRS monitor), was bought by Covidien, Inc. One of their first orders of business was to terminate all existent research agreements. Over the 1st quarter of Period 2, Dr. Shuler worked with Covidien to try to find a path forward. This was unsuccessful. Simultaneously, we explored the possibility of a new collaborating relationship with Nonin, Inc. maker of the Equanox oximeter, which is a NIRS oximeter with equivalent functional claims and FDA approval. This second option has proven to be the best. In vetting this option, J+M Shuler performed an IRB approved study which recapitulated our control cohort from Phase 1, and this showed that the devices performed equivalently; in fact the variance of the data was significantly less for the Equanox device. This was reported at the 2011 ATACC meeting. (Appendix 3 and 4) Further, the Equanox has been chosen by the Major Extremity Trauma Research Consortium (METRC), another USAMRAA funded research project, to be their NIRS oximeter for their complimentary acute compartment syndrome studies.

This task was re-completed in March 2011, as J+M Shuler secured a signed letter of support from Nonin, Inc. to participate in our animal studies and Phase 2 clinical study as well as commitment to developing their current off-the shelf oximeter to a FDA approved device for diagnosing acute compartment syndrome. This letter of support has been submitted to USAMRAA.

4b. Begin reduction to practice process. Ongoing

4c. Produce final prototype for use in completion of Phase 1, all of Phase 2 and the investigational clinical study to be supported by a future grant. Ongoing - The current embodiment, more specifically the spectroscopy technology is mature and ideal for our intended indication. In this light, we have a final prototype. There are still planned small physical improvements, for example, increasing the number of ports per machine, but these improvements will not affect the results of our planned studies.

4d. Respond to provider feedback re: functionality and industrial design - Completed. The non-PI/Al providers had limited operational exposure with the NIRS equipment in Phase 1. There were no significant comments for areas of improvement. In our experience with the device, the only two significant physical improvements needed are the addition of more ports to a single machine, so that a single patient can be monitored by a single machine, and "horse-tailing" of leads, such that 4 sensors connect to a single cable about 1 foot or less from the patients leg and that cable then runs back to the device, to cut down on cable clutter in the current system. Both of these changes are small and will not affect our results. To get broader feedback, we have included provider feedback into the CRF for the Phase 2 study. The primary product development piece to occur over the course of this grant and in work to follow the conclusion of this grant will be the development and then validation of a diagnostic algorithm, for which a new FDA indication will be applied that approves the use of this device as a diagnostic tool for acute compartment syndrome.

TASK 5. Coordination between study sites

5a. Bi-annual collaborators meeting – Ongoing. Given the transition from LRMC as a research site for Phase 2, to the Atlanta area, we have increased on-site visits to 3/year.

5b. Conduct weekly VTC (Telcon) for LRMC/J+M Shuler, and OIF/OEF during Phase 2 - Ongoing

5c. Rapid interpretation of weakness in the design and function of sequential NIRS pad prototypes and NIRS monitoring algorithms. – Ongoing. The device is in a state where it is and has been fully ready for testing in our studies. It will probably undergo some minor physical improvements with time. The major improvement will be the design and validation of a diagnostic algorithm based on NIRS values. This process is ongoing and will continue past our grant period. This process will ultimately require validation in a prospective interventional trial.

5d. Coordinate response to FDA requests for information during approval process: Ongoing. LTC David Shoemaker, Marieann Brill and “Decision Gate” are all involved in USAMMDA’s sponsorship of this project and the creation/maintenance of a FDA compliant medical monitoring program for the 3 clinical sites in Phase 2. As a result, this Phase 2 study will be permissible for inclusion in the “burden of proof” submission for our ultimately new FDA 510k approved indication.

5e. Insure mandatory reporting to SAMMC, ISR & USAMRMC is maintained: Ongoing and in good standing.

Task 6. Future Research Endeavors –At the completion of tasks 1-5 we will have a publically available, FDA-approved monitoring device with solid basic science and initial clinical research support. The main outcome of this task is to start the next step, which is the creation and validation of NIRS-base clinical guidelines for the diagnosis and treatment of acute compartment syndrome to support a new FDA indication for the Nonin Equinox as a DIAGNOSTIC device, on top of its currently approved monitoring indication. This task requires clinical investigational trials that will follow the conclusion of this grant.

Review of Clinical Studies:

Review of Enrollment Status at end of 4th quarter, Period 2:

Phase 1 (Cohort 1, 2, 3) – COMPLETE - Total of 135 patients

Phase 2 (Cohorts 1, 2A, 2B, 2C) – NOT STARTED – Total 120 patients

Problem Areas:

1. Denial of Phase 2 Protocol – We developed and validated an acceptable alternate course of action.
2. Transition to an FDA IDE trial – We are meeting this challenge.
3. Termination of Contract Somanetics/Covidien – We obtained a new vendor and validated their technology.
4. TRUE Foundation went bankrupt and we have switched our grant management to the Geneva Foundation.

KEY RESEARCH ACCOMPLISHMENTS

1. Successfully completed 100% enrollment for Phase I and Part 2 Animal Studies.
2. Validated the contralateral leg as the ideal control for patients with unilateral lower extremity injuries. This is useful due to high between-patient and within compartment variability of NIRS values over time. The constant in NIRS values over time is a <3% variance between contralateral, like leg compartments (i.e. The left anterior compartment in the normal setting should be the same or no more than 3% different than the right anterior compartment. Based on Dr. Shuler's prior clinical work with NIRS monitoring in the setting of compartment syndrome 12-15% differences between compartments is clinically significant.)
3. Described correlations between NIRS values of the lower extremity and those of various compartments of the upper extremity, which will be essential for patients with bilateral injuries.
4. Demonstrated equivalence and/or superior reliability in monitoring oxygen saturations in the leg with the Nonin Equanox 7600 oximeter, compared to the Somanetics INVOS oximeter.

Specific to our Animal Studies:

1. NIRS values decreased significantly compared to baseline values at all time points once 20 mmHg perfusion pressure was reached and did not return to baseline until after fasciotomy.
2. There was a significant negative correlation between intracompartmental pressure and NIRS measurements ($r=-0.79$, $p<0.0001$).
3. There was a significant positive correlation between perfusion pressure and NIRS measurements ($r=0.80$, $p<0.0001$).
4. NIRS was able to detect decreased tissue oxygenation at every perfusion pressure decrease and subsequent increase following pressure relieving fasciotomies
5. 5-10 minutes after fasciotomy, perfusion pressures and NIRS values returned to baseline.
6. Our animal model has proven our research hypothesis: NIRS values decrease as compartment pressures increase to the point of compartment syndrome and NIRS values increase after fasciotomy, suggesting that releasing the tissues restores normal perfusion to the area.

REPORTABLE OUTCOMES (Period 2)

Accepted/Presented Abstracts:

Freedman BA, Jackson KL, Cole AL, Shuler MS... Do Skin Pigmentation and Hair Affect Near-Infrared Spectroscopy Assessment of Leg Compartment Syndrome. Poster Presentation at 2011 Southern Orthopaedic Association Annual Meeting, Kona, HI, 22 July 2011; 2011 American Academy of Orthopaedic Surgeons Annual Meeting San Diego, CA 15-19 February 2011; 2011 Extremity War Injuries Symposium (break-out session) 19-20 Jan 2011 and 2010 Annual Society of Military Orthopaedic Surgeons Meeting, Vail, CO, 13-17 December 2010.

Cole AL, Herman RA, Heimlich JB, Ahsan S, Freedman BA, Shuler MS. Ability of near infrared spectroscopy to isolate muscle compartments of the upper extremity. American Academy of Orthopedic Surgeons Annual Meeting, February 7-11, 2012, San Francisco, California. (Paper presentation)

Reisman W, Shuler M, Cole A, Whitesides T, Moore T. Relationship between near infrared spectroscopy and intracompartmental pressures in the leg: a model for acute compartment syndrome. Southern Orthopaedic Association 27th Annual Meeting, June 16-19, 2010, Fajardo, Puerto Rico; Poster 30. (Poster presentation)

Freedman B, Cole A, Shuler M, Jackson K, Owens L, Lackie D. Do skin pigmentation and hair affect near-infrared spectroscopy assessment of leg compartment syndrome. Advanced Technology Applications for Combat Casualty Care 2011 Conference, 15 - 18 August 2011 Fort Lauderdale, Florida. (Poster presentation)

Cole AL, Shuler MS, Robinson MA, Freedman BA. Comparison of near infrared spectroscopy values between compartments of the lower extremities. Advanced Technology Applications for Combat Casualty Care 2011 Conference, 15 - 18 August 2011 Fort Lauderdale, Florida. (Poster presentation)

Submitted Abstracts:

Cathcart C, Shuler M, Freedman B, Reynolds L, Cole A, Budsberg S. Non-invasive NIRS versus invasive direct pressure monitoring of acute compartment syndrome in a porcine model. Orthopedic Research Society, February 4-7, 2012, San Francisco, California.

Cathcart C, Shuler M, Freedman B, Reynolds L, Cole A, Budsberg S. Non-invasive NIRS versus invasive direct pressure monitoring of acute compartment syndrome in a porcine model. American Orthopaedic Association Annual Meeting, June 27-30, 2012, Washington, DC.

Manuscripts in Preparation:

Jackson KL, Cole AL, Potter BK, Shuler MS, Freedman BA Identification of optimal control compartments for serial near-infrared spectroscopy assessment of lower extremity compartmental perfusion (Submitting to Journal of Bone and Joint Surgery)

Shuler MS, Freedman BA. Near-Infrared Spectroscopy in Acute Compartment Syndrome. (Invited submission Techniques in Orthopaedics)

Shuler MS. Technique of Fasciotomy: Upper arm and forearm. (Invited submission Techniques in Orthopaedics)

Freedman BA, Shuler MS. Techniques for Fasciotomy Closure. (Invited submission Techniques in Orthopaedics)

CONCLUSION:

This continues to be a very ambitious project for LRMC and the forward deployed research team, but at the same time it remains a much needed one. We had a significant issue with the originally submitted Phase 2 protocol application, which required months of negotiation and response to overcome. In the end, we have an excellent plan and all of the data collected in our Phase 2 study will be FDA compliant and available for inclusion in the future 510k application.

Similar administrative situations occurred in Period 1 with Phase 1. We continue to negotiate these hurdles. As our abstracts demonstrate we are already starting to generate an abundant amount of reportable information that contributes to our overall grant aims.

This completed data collection on control subjects has led to a greater understanding of the normal performance of NIRS values over time, which will be invaluable in establishing non-normal NIRS values in order to anticipate and recognize (diagnose) an impending compartment syndrome, the ultimate goal of this research.

This year has produced the first step in reducing missed cases of ACS, as well as unnecessary fasciotomies, among soldiers injured in battle.

This study confirms that the contralateral uninjured leg or, in patients with bilateral leg injuries, the volar forearm, are the ideal control sites to compare to the traumatized leg. These data suggest that NIRS values may be affected by a patient's skin pigmentation. However, shaving the leg hair of male patients does not appear to affect NIRS values.

We are happy with our progress. While we continue to strive to meet all timeline goals on time and below budget, we will fall short with the initiation of Phase 2. We will continue to be flexible and adaptive.

REFERENCES:

None

Appendix 1: REVISED STATEMENT OF WORK:

Updated Overview:

At this point, we are almost 8 quarters into what was originally to be a 12 quarter project (3yr), and we have completed or nearly completed the following original tasks: 1(a-g), 2 (a-c), 3 (a-d), 4 (a-d), 5 (a-c). Thus, despite the setbacks we have sustained regarding Task 2 and some elements of Task 4 and 6, which will be outlined below, at the 23 month mark, we have delivered or are in the final process of delivering all tasks (excluding Tasks 2) due by this point, according to the original SOW.

At this point in time, due to reasons beyond our control and despite our best efforts to the contrary, Task 2, 4 and 6 will need to be modified.

Task 2 was the most critical of our 6 tasks, as this was the Phase 2 human use study, which would define the diagnostic thresholds and reliability of our COTS (commercial off-the-shelf) NIRS monitor for detecting acute compartment syndrome (ACS). The need for a diagnostic device for detecting ACS in combat injured soldiers was clearly laid out in our original grant application and this continues to be a critical unmet need for the military and civilian sector. In the process of reviewing our Phase 2 protocol application, the MRMC IRB made an independent decision to petition the FDA for a pre-IDE determination on our protocol. This resulted in a recommendation for the protocol to be performed under an abbreviated IDE status, which effectively eliminated the possibility of performing this study or the 3 other DoD funded studies under similar circumstances in the combat zone. The reason being, that a significant proportion (much higher than in the civilian sector) of patients traumatically injured in combat are unable to provide their own legally effective consent. In the absence of the FDA IDE requirement, this study clearly met the "Common Rule" standards for waived consent research (minimal risk protocol, nonsignificant risk device and no way to perform the study with consent) and the protocol was approvable in this fashion, but the addition of FDA IDE status, required consent. As a result, in Sep '10 we ran a sample of cases presenting to Craig Joint Theater Hospital in Bagram, Afghanistan, and felt that we would be able to meet our enrollment target on time, with required informed consent. Thus we modified our Phase 2 protocol to include consent. Then the hospital commanders in Afghanistan, pulled their support, as they do not require documented informed consent for many of the trauma surgical operations performed in their facilities, thus they felt this would set up a dual standard and compromise medical operations. A third tactic was then attempted, in which LTC Laura Brosch of the MRMC IRB, in coordination with LTC Shoemaker of USAMMDA, petitioned the FDA for an exception to policy, to allow FDA sponsored research to occur in the combat theater without waived consent. On 25 Feb 2011, Dr. Brosch ended our 10-month IRB approval process, when she broadcasted the final results of this their meeting with the FDA on 23 Feb 2011. No exception to policy is possible short of an act of Congress. Thus, MRMC has effectively placed a moratorium on prospective human use research in the combat zone using medical devices. Since our Phase 2 study was scheduled to occur in the combat zone, this meant we needed to develop an alternate course of action (COA). We took the 30 days following the email notification from Dr. Brosch, to not only create an alternate COA that allows us to reach all stated aims of this grant, but also we vetted this COA. Our proposed alternate Task 2 is to perform the equivalent methodology, with only military specific aspects of the original protocol modified, in a Phase 2 study at Grady Memorial Hospital (GMH) and Atlanta Medical Center (AMC), the two Level-1 trauma centers for the Atlanta metro-area. In addition, we would also initiate the Phase 2 protocol at Athens Regional Medical Center (ARMC), the Level-2 trauma center receiving most north-Georgia trauma cases that are not sent to the Atlanta trauma centers. Further, ARMC is co-located with J+M Shuler, which will allow cross-productivity for the research assistant hired for this location. Grady is the hospital where Dr. Michael Shuler (co-PI) performed the original work demonstrating the role for NIRS monitoring in the setting of severe leg injury with and without compartment syndrome. Further, these two facilities both have residency programs and are well known for their contributions to the orthopaedic trauma literature, especially in the field of compartment syndrome. We have secured commitment letters from the directors of orthopaedic trauma from both facilities. Further we have translated our Phase 2 protocol into each facility's IRB format and are prepared to submit these protocols for review. These studies will be conducted with an informed consent requirement. Further, each site has reviewed its trauma registry and demonstrated that we can meet our planned enrollment goal within 12 to 18 months of initiating this study following local and AHRPO IRB approval. Further, both institutions are familiar with using and studying NIRS monitors in the setting of ACS. We expect that with immediate approval from USAMRAA we could submit and have local IRB approval within 2 months. Further, since the approved protocols are based off minimal modifications to our original Phase 2 protocol, which was "approved" pending the result of the FDA determination, the transit through 2nd level review should be short. Thus, we feel it is entirely realistic to have this project up and running at both sites by the early part of the 1st quarter, Period 3. This prolonged IRB process has cost our project 1 year of lost time and paid wages, which cannot be overcome. Given the above facts, we are requesting a grant modification to extend the overall grant 1 additional year and increase the overall budget. We are confident that this modification will allow us to accomplish all of the tasks we originally submitted.

Our Phase 2 study is the pivotal portion of this overall research project. Without this study, we cannot move further towards the ultimate goal of producing an FDA approved device for diagnosing ACS. Further, its impact reaches beyond our study and directly impacts the success of the Major Extremity Trauma Research Consortium's ACS Study, for which Michael Shuler, along with Andrew Schmidt are PIs. The follow-on METRC study will use our findings, specifically diagnostic NIRS threshold values and oximetry response to fasciotomy in the setting of ACS as integral criterion in diagnosing ACS. These studies are complimentary, not redundant. Further, our collaborative efforts over the last 12 months have insured that these successive studies are maximally synergistic.

Original Overview:

The essential facilities and clinical support needed to start this project are in place. Thus commencement of the project is dependent upon acquisition of funds and "DoD second level approval (USAMRMC-HRPO)" for the Phase 1 human use protocol. We have received IRB approval from two DoD levels to date--San Antonio Military Medical Center (SAMMC) and DoD Clinical Investigator Regulatory Office (CIRO). CIRO is the US Army HQ or second level review required on Pg 10-11 of the USAMRMC Guidelines for Investigators PDF (<https://mrmc.amedd.army.mil/docs/rcq/GuidelinesforInvestigators.pdf>). We currently have hiring actions for the three research coordinators, which are the only full-time (100%) salaried employees from the grant. We are finalizing contracts with the consultants listed in the original grant budget justification PDF. All hourly rates and total time commitments listed in the original budget justification are agreed to and fixed. All research related equipment (INVOS monitors and leads, Stryker Pressure gauges, DermatoSpectrometer, BX 2000 Body Fat Ultrasound Monitor) is immediately available for purchase. When funds are released we will obtain these items. Animal use studies will not commence until the 2nd year of this study. IACUC approval, CRADA agreements and expenditures for this portion of the study will come in the 2nd and 3rd year. The following is an outline of milestones and work needed to complete the studies and product development described in our original CDMRP grant application. Estimated milestones are based on time zero being 1 OCT 2009, which is our planned date for initiation of the grant.

Investigators:

- PI - Brett Freedman, MD - US Army, Landstuhl Regional Medical Center, Germany
- AI - Michael Shuler, MD – J+M Shuler, Atlanta, GA
- Lead Research Coordinator – Ashley Cole, MPH
- LRMC Research Coordinator - TBD
- NIRS Research Team. – Under the alternate COA – the Phase 2 study will move to GMH, AMC and ARMC, where we will include 1 PI (unpaid investigator) and 1 research coordinator (paid position) per site. A research orthopaedic surgery resident (unpaid investigator) will also be assigned at GMH and AMC.
- University of Georgia College of Veterinary Medicine (Athens, GA) - Site for all animal studies.
 - PI: Steven Budsberg
- Remaining personnel identified in our budget justification are consultants

Study Sites:

- LRMC – Primary site for all Phase 1. Overall coordinating center for entire project.
- GMH, AMC, ARMC – Proposed Phase 2 Study Sites
- J+M Shuler – Primary site for all product development and FDA approval
- University of Georgia – ONLY site for animal use studies

Task 1. Human Use Study → Phase 1 (LRMC) (N=up to 150 subjects) – (UNCHANGED AND COMPLETED) Prospective Observational Study, Primary outcome measure will be correlation, diagnostic accuracy and reliability of NIRS monitoring of legs with and without injury. The results of Phase 1 and Phase 2 studies will satisfy Aim 1 and support elements of Aim 3

- 1a. Create and Submit SAMMC Human Use IRB Protocol Application, Principal Investigators Complete CITI Training (Completed).
Obtain second level DoD IRB approval. (Ongoing)
- 1b. Obtain clearance and impact statements from: (Ongoing – month 3)
 - LRMC Commander
 - LRMC DCCS
 - LRMC Chief, Div. of Surg
 - LRMC Chief, Trauma Program
 - LRMC Research Review Committee
 - ERMC MEDCOM
 - CIRO
 - USAMRMC – 2nd Level DoD IRB
- 1c. Hire 2 Research Coordinators (LRMC site) and 1 Project Manager (J+M Shuler site)
(Prior to starting Phase 1)
- 1d. Initiate Patient Enrollment (months 0-3)
- 1e. Conduct Phase 1 Prospective Observational Study (months 0-9)
- 1f. Analyze Data, Provider Feedback and Amend Phase II Methodology as needed
(months 3-15)
- 1g. Present/Publish Results of Phase 1 (months 9-15)

Task 2. Human Use Study → Phase 2 (Atlanta/Athens + OIF/OEF) (N=120 Subjects) – Prospective Observational Study with similar methodology and outcome measures to Phase 1, the significant difference, is that Phase 2 enrollment will occur more proximate to the time of injury at 1 of 3 study sites in Georgia.

- 2a. Create and Submit local institution Human Use IRB Protocol Application (months 21-24))
- 2b. Obtain clearance and impact statements from: (months 21-27)
 - GMH – Chief of Ortho Trauma (Completed)

AMC – Chief of Ortho Trauma (Completed)

- 2c. Recruit lead investigators for GMH, AMC, ARMC (Completed)
- 2c. Recruit research staff for GMH, AMC, ARMC 21-24 months
- 2b. Conduct Phase 2 Prospective Observational Study (months 24-42)
- 2d. Analyze Data, Provider Feedback (months 39-45)
- 2e. Present/Publish Results of Phase 1 (months 42-48)

Task 3. Animal Use Study → Pig Studies (University of Georgia) (N=100 adult pigs)

(UNCHANGED AND IN PROGRESS) *Note change in location from original grant. UGA has better capabilities for conducting animal studies. Likewise, it is geographically co-located with our lead associate investigator (Michael Shuler). The USAF will internally and in collaboration conduct additional in-flight related trials as needed. These studies may occur through UGA as well or through USAF collaborative labs at the University of Cincinnati.

Animal Use Experimental Studies using a validated swine model. Primary outcome measure will be change in NIRS values following alterations to in physiological state and induced injury. The results of this task will satisfy Aim 2 and support Aim 3

- 3a. Create and Submit UGA IACUC Protocol Application (month 6-9)
- 3b. Obtain approval from UGA IACUC and USAMRMC ACURO (month 9-15)
- 3c. Initiate animal studies outlined under Aim 2 (month 15)
- 3d. Conduct animal studies outlined under Aim 2 (month 15-24)
- 3e. Analyze data, Formalize contributions to FDA approval packet (month 24-30)
- 3f. Present/Publish Results of Aim 2 Animal Studies (months 24-30)

Task 4. Reduction to Practice and FDA Approval Process – Product development and regulatory approval will be conducted through the J+M Shuler site, in direct collaboration with the LRMC clinical research and UGA animal research sites and Nonin, Inc. We have officially switched COTS vendors from Somanetics, Inc to Nonin, Inc. The Nonin Equanox oximeter is an equivalent, if not superior NIRS oximeter. We have recapitulated our Phase 1 control trial at the J+M Shuler site under an IRB approved protocol (St Mary's Healthcare System – Approved 1/13/11) and found that the Equanox can reliably detect somatic tissue oxygen saturation values in the leg, which is consistent with its stated FDA approved indication. Further, Equanox will be the NIRS oximeter used in the METRC ACS study. The primary outcome of this task is final prototyping and preparation for FDA approval via the 510K application process which will allow for public sale and distribution of this product following an interventional clinical study requested by the FDA to support an FDA application for a diagnostic indication. Successful completion of this task will satisfy Aim 3.

- 4a. Finalize product development relationships between Nonin, Inc and J+M Shuler (Completed)
- 4b. Begin reduction to practice process. Current embodiment is not ideal, but the data acquisition, fidelity is mature. Change pad configuration, improve pad adhesion, increase number of data-ports per machine. Synchronize data between devices and between physiological monitors. (Ongoing; month 18 – 48+)
- 4c. Produce final prototype for use in completion of Phase 1, all of Phase 2 and the interventional clinical study to be supported by a future grant. (Completed)
- 4d. Respond to provider feedback re: functionality and industrial design (Ongoing; months 18-45)
- 4e. Work with Nonin, Inc to complete the final development of a NIRS-based ACS monitor to a market-ready, FDA approvable status (months 24-48+)
- 4f. (Conduct Phase 2 under abbreviated IDE requirements) (months 24-42)
- 4g. Respond to and conduct additional studies/product development as requested by FDA (months 39-48+)
- 4h. Good Manufacturing Practice (GMP) authentication and establishment of distribution system (months 48+)
- 4i. Submit application for FDA 510k Approval (48+)
- 4j. Initial production of validated NIRS monitoring system for public use (month 48+)

Task 5. Coordination Between Study Sites (LRMC and J+M Shuler) – Two simultaneous objectives will be promoted over the course of this grant—(1) establishment of the burden of proof for NIRS monitoring of compartment syndrome and (2) final prototyping and FDA approval of a working NIRS monitoring device. As stated in quarterly and annual reports to USAMRAA – the primary innovation/improvement will be in the incorporation of a NIRS-based validated diagnostic algorithm. This algorithm will be defined through the analysis of Phase 1 and 2 results, confirmed in the METRC ACS study and then tested in an interventional study to follow this grant period. This 3-tier approach reflects the FDA recommendations from Aug 2010 for the development and approval of a NIRS based diagnostic device for detecting ACS. Regular coordination between the primary clinical research location (LRMC) and the product development primary location (J+M Shuler) is essential to completion of Aims 1 and 3. This coordination will be made slightly more challenging, given the transfer of clinical studies from LRMC to Georgia. As a result, the overall PI, will make 3 annual visits to Georgia over the next 12 quarters to oversee successful completion of animal testing and initiation and completion of Phase 2 clinical studies.

- 5a. Tri-annual collaborators meeting (Atlanta, GA)
- 5b. Conduct weekly conference with LRMC/J+M Shuler/GMH/AMC during Phase 2

- 5c. Rapid interpretation of weakness in the design and function of sequential NIRS pad prototypes and NIRS monitoring algorithms. (month 24+)
- 5d. Coordinate response to FDA/USAMMA requests for information during approval process (month 21+)
- 5e. Insure mandatory reporting to SAMMC, ISR & USAMRMC is maintained (quarterly)

Task 6. Future Research Endeavors – At the completion of tasks 1-5 we will have a publically available, FDA-approved device with solid basic science and initial clinical research support. The main outcome of this task is to start the next step, which is the creation and validation of NIRS-based clinical guidelines for the diagnosis and treatment of acute compartment syndrome. This task transitions to clinical investigational studies.

- 6a. Create NIRS-based clinical guidelines based on results of Aim 1-3 (months 39-48)
- 6b. Complete and submit a prospective clinical investigational study IRB application to validate NIRS-based clinical practice guidelines (Future Project)
- 6c. Analyze data, Publish/Present, Revolutionize diagnosis and treatment of ACS (months 48+).

Appendix 2: 2011 ATACC Accepted NIRS Abstracts

Do skin pigment and hair affect near-infrared spectroscopy assessment of leg compartment perfusion?

Authors: Freedman BA, Shuler MS, Jackson KL, Owens LE, Lackie DA, Cole AL, Ethington A, Reisman W, Whitesides T.

Introduction: ACS is a clinical diagnosis, with poor inter/intra-rater reliability. Currently, patients with ACS are being missed, and patients without ACS are being unnecessarily fasciotomized. This study is part of a multi-phased DoD research project, seeking to validate a continuous, noninvasive NIRS ACS monitor for military-use. The purpose of this study is to evaluate the impact of skin pigment and hair on NIRS values in normal controls.

Methods: Forty-four healthy volunteers (14 M; 30 F) were monitored for two 1-hour continuous sessions, using a standardized protocol, which placed NIRS leads over the 4 compartments of each leg, recording NIRS values (% saturation) every 30sec. Additionally, the dorsal and volar forearm compartments and deltoid were monitored. Colorimeter readings of skin pigmentation from two probes were used to document skin pigmentation. The NIRS values for each compartment were then compared to NIRS readings from corresponding compartments and colorimeter values.

Results: NIRS values in left and right leg are highly conserved. The data is very reproducible with an insignificant (<1%) average difference between day 1 and 2. Upper extremity NIRS values were strongly correlated to leg values in the following order volar ($r=0.65$ to 0.71), dorsal ($r=0.36$ to 0.60) and deltoid ($r=0.42$ to 0.51). A moderate negative correlation was observed between melanin and NIRS values, while "L" values were positively correlated. Shaving did not affect NIRS values.

Conclusions: This study confirms that the contralateral uninjured leg or, in patients with bilateral leg injuries, the volar forearm, are the ideal control sites to compare to the traumatized leg. These data suggest that NIRS values may be affected by a patient's skin

Comparison of near infrared spectroscopy values between compartments of the lower extremities

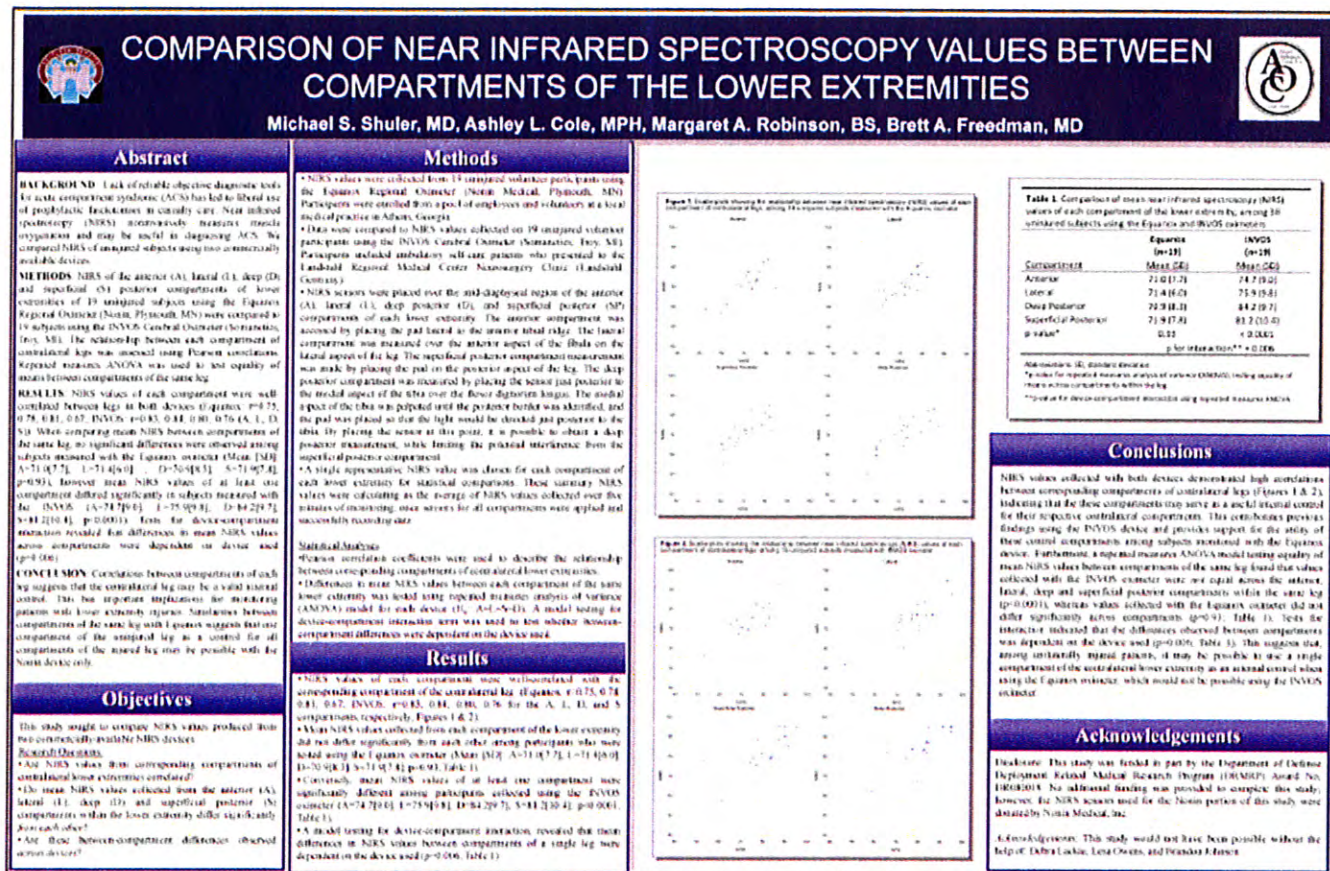
Michael S. Shuler MD, Ashley L. Cole MPH, Margaret A. Robinson BS, Brett A. Freedman MD

BACKGROUND: Lack of reliable objective diagnostic tools for acute compartment syndrome (ACS) has led to liberal use of prophylactic fasciotomies in casualty care. Near infrared spectroscopy (NIRS) noninvasively measures muscle oxygenation and may be useful in diagnosing ACS. We compared NIRS of uninjured subjects using two commercially available devices.

METHODS: NIRS of the anterior (A), lateral (L), deep (D) and superficial (S) posterior compartments of lower extremities of 19 uninjured subjects using the Equanox Regional Oximeter (Nonin, Plymouth, MN) were compared to 19 subjects using the INVOS Cerebral Oximeter (Somanetics, Troy, MI). The relationship between each compartment of contralateral legs was assessed using Pearson correlations. Repeated measures ANOVA was used to test equality of means between compartments of the same leg.

RESULTS: NIRS values of each compartment were well-correlated between legs in both devices (Equanox: $r=0.75, 0.78, 0.81, 0.67$; INVOS: $r=0.83, 0.84, 0.80, 0.76$ (A, L, D, S)). When comparing mean NIRS between compartments of the same leg, no significant differences were observed among subjects measured with the Equanox oximeter (Mean [SD]: A=71.0[7.7], L=71.4[6.0], D=70.9[8.3], S=71.9[7.8]; $p=0.93$), however mean NIRS values of at least one compartment differed significantly in subjects measured with the INVOS (A=74.7[9.0], L=75.9[9.8], D=84.2[9.7], S=81.2[10.4]; $p<0.0001$). Tests for device-compartment interaction revealed that differences in mean NIRS values across compartments were dependent on device used ($p=0.006$).

CONCLUSION: Correlations between compartments of each leg suggests that the contralateral leg may be a valid internal control. This has important implications for monitoring patients with lower extremity injuries. Similarities between compartments of the same leg with Equanox suggests that one compartment of the uninjured leg as a control for all compartments of the injured leg may be possible with the Nonin device only.



Appendix 3:

Technology Comparison

	Hutchinson Inspectra	EQUANOX Advance	Invos	Foresight
Inter/Intra Sensor Repeatability Accuracy*	?	+/- 2	?	?
Transportable? (weight x battery life)	Y	Y	N	N
Durable (Drop-Test, No/Low Maintenance)	N	Y 1meter, No Maintenance	N No Drop Test Maintenance - Fuses, CPU Maintenance, Battery Replacement	N No Drop Test Maintenance - Fuses, Fan Cleanings, Battery Replacement Fiber Optic Cables

Transportability – Weight	4kg	1kg	6.85kg	6.85kg
Transportability – Battery Life	2 hours	3 hours	20 min	1.5 hours
Temp Operating Range	50 to 104 F	23 to 104 F		
Storage/Transport	0 to 140 F	-22 to 158 F		

* Based on package insert and instructions for use.

Technology Comparison

	Hutchinson Inspectra	EQUANOX Advance	Invos	Foresight
Sensors able to be placed in Proximity	?	Y	N	?
# of channels	1	4 Up to 6 (2012)	4	2
Ambient Light tolerant*	?	Y	N	N
Instant Reading (<2 seconds)	Y	Y	N	N
Smart sensor/calibration (no need for patient data entry at start up)	Y	Y	Y	N

Evaluation Criteria

	Description/Importance
Somatic Use	Approved indication for use over muscle bed – core for this application
Cerebral Application	Approved indication for cerebral use – adds to potential future capabilities and minimizes need for additional solutions
Stable Signal	Reduced signal variation during readings – some technologies vary +/- 10 points within the span of seconds, potential due to signal scattering in the physiology
Minimized Signal Disruption	Reduced signal interruptions or signal loss, due to the presence of shielding in cable & sensor
Minimized Skin Color Effects	Ability to strip surface artifacts comprising accuracy in varying skin colors/tones
Maximized Patient Performance	Reads on wide range of patients, with no known patient set / type which does not read reliably
Sensors able to be placed in proximity	Sensors can be placed close to each other without risk of interference/signal loss, i.e., sensor LEDs synchronized to ensure cross sensor light contamination is prevented