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TITLE:Supplemental Perioperative Oxygen to Reduce Surgical Site Infection after High-Energy Fracture Surgery

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14. ABSTRACT Our study is a multi-center prospective randomized treatment trial investigating if supplemental perioperative oxygen use will reduce surgical site infection after surgery on fractures with a high risk of infection. The study utilizes the DOD-funded Major Extremity Research Consortium (METRC). The study population is calcaneus, pilon, and tibial plateau fractures. During the first year we created a protocol committee, designed and approved the protocol and CRFs, obtained IRB approval. We originally enrolled 1000 patients at 29 centers. Based on feedback from the DSMB we increased our enrollment goal to 1171 and completed this in March of 2018. Follow up rate has been strong with 88% at 12 months. We now only await final follow up this spring to complete the study.

15. SUBJECT TERMS
Supplemental perioperative oxygen, surgical site infection, fracture fixation complications

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1. INTRODUCTION:

The overall scope of this project is to address the treatment of high-energy military fractures, which has historically been shown to have poor outcomes and continues to be associated with high rates of infection. Perioperative oxygen has been studied in several thousand general surgery patients and shows promise to reduce surgical site infection in these patients. This technique might have tremendous public health consequences as it is already available in all operating rooms throughout the world and has almost no cost or risks. Outside of a pilot study performed at our institution (Reference 1), this technique has not been investigated in high energy fracture patients that are at such risk for surgical site infections. Our study is a well powered multi-center randomized controlled trial investigating the use of supplemental perioperative oxygen to address the problem of infection in these at risk patients. Our hypothesis is that the use of supplemental perioperative oxygen for fractures at high risk for infection will reduce infection rates and therefore improve outcomes compared to treatment without this technique. The study population is patients with high energy tibial plateau, pilon (distal tibia), and calcaneus fractures. The results of this trial have the potential to reduce surgical site infection within both the military and civilian sectors and therefore improve patient outcomes from these potentially devastating injuries.

2. KEYWORDS:

Supplemental perioperative oxygen, surgical site infection, fracture fixation complications, complication reduction, pilon fracture, calcaneus fracture, tibial plateau fracture

3. OVERALL PROJECT SUMMARY:

The fifth year of the grant built on the success of the first four years. During the second year we the study and began enrolling. In the fifth year we enrolled the original goal of 1000 patients (1000th patient enrolled in mid October 2017). Based on feedback from our DSMB we have decided to increase the enrollment goal and in the sixth year we met our revised enrollment goal with 1171 (53% of those eligible). Follow up rates have been strong: 3month (94%), 6 months (88%) and 12 months (88%). Seven hundred thirty-eight patients have followed up to one year to date. The study is performing well and there are no known barriers to study success at this time as we await final follow up this spring.

Specific Aim #1 Compare the proportion of surgical site infections within 6 months in patients treated with Supplemental Perioperative Oxygen compared to those treated without Supplemental Perioperative Oxygen.

1.1.Finalize Study Protocol

1. 1.1 Protocol Committee Creation

The Protocol Committee was successfully defined and formed during the first quarter of year one in keeping with METRC (Major Extremity Trauma Research Consortium) guidelines as described in previous reports. The committee for this study is detailed in Appendix 1. We designed to the committee to make sure it represents leaders in all fields that the study will involve. The committee for this study encompasses:

1. The P.I.
2. Orthopaedic Trauma Surgeons, from METRCg sites.
3. Infectious Disease Attendings, with expertise in orthopaedic infections
4. Two Anesthesiologists
5. Two PACU nurses
6. One Research Coordinators from Participating sites
7. One Research Coordinator from the PI's site
6. Two METRC Coordinating Center Staff (expertise in study design)
7. One METRC PI (Castillo)

The Protocol Committee members was defined, invited, and formed during the first quarter.

1.1.2. Protocol Development

***Protocol Design*:**

During the first year the protocol was designed and finalized (included in Appendix 2 of first year report).

Protocol Approval History:

***Protocol Committee Approval*:** The final protocol for IRB submission was approved by the protocol committee on January 2013.

***METRC Steering Committee Approval*:** The protocol was circulated to the entire METRC Steering Committee. The final protocol for IRB submission was unanimously approved by METRC steering committee vote on February 2013.

1.2 Finalize/Adapt/Test Study Materials

CRF/SOP Development

CRF/SOP Design The Case Report Forms (CRFs) were developed in parallel to the protocol development along a similar timeline, leveraging previous METRC infrastructure to maintain uniformity with other METRC projects and leveraging on our experience with our pilot study (Reference 1) and other METRC studies.

CRF's were included in the annual report of year 1.

IRB Submission: The CRFs have been part of the IRB submission at sites that require it.

1.3 Train Study Coordinators

Study coordinator training occurred through both online live training (September 6, 2013) and in person training at the national meeting (October 9, 2013).

The presentation materials for local site training of anesthesia and recovery room nursing staff have been developed and completed by a subgroup of the protocol committee. This training will occur at each site just prior to first patient enrollment.

Additionaly the PI and key personell from the protocol committee and METRC coordinating center contact each site and the local investigators for phone meetings once study enrollment begins to ensure that all questions are answered and to address any site specific issues.

1.4 IRB Approval at First Site (Milestone #1)

This task was accomplished in year one as detailed in prior reports.

IRB Approval at PI Site: The IRB submission was approved by University of Maryland School of Medicine on June 3rd 2013. A very minor modification required by the DOD IRB required IRB resubmission and this modification approval was received on October 15, 2013.

IRB Approval at METRC CC: The original IRB submission was approved by Johns Hopkins April 3, 2013. Revised protocol was approved on September 15, 2013 after modification for aforementioned minor changed required by DOD.

IRB Approval at DOD: DOD approval was obtained October 28, 2013.

DOD IRB Approval of PI Site: Pending

Assuming a relatively rapid approval of our IRB approved protocol by DOD, we are well positioned to begin enrollment at the first site soon.

1.5 IRB Approval at All Sites

The process of IRB approval at other sites has proceeded well in the past year. Of the 19 participating sites, 12 have local and DOD IRB approval and are currently enrolling, 4 are certified to begin enrollment, and 3 are in various stages of IRB approval process. We anticipated IRB approval at all sites in next quarter.

1.6 Enroll First Patient (Milestone #2)

The first milestone was accomplished during this last year on January 7, 2014 at the PI's site.

1.7 Enrollment

Enrollment is underway and proceeding well. We enrolled all of our original goal of 1000 patients of our original sample size. As anticipated, site enrollment peaked at a pace of nearly 600 per year (see Appendix 2); once the VANCO study completed enrollment. This is because the METRC VANCO study competes for these same patients and runs at 35 METRC sites. The plan has always been to complete VANCO enrollment first (which was accomplished) and then immediately switch those sites back to OXYGEN (which was also accomplished). The high volume sites switching to OXYGEN allowed us to quickly reach a high enrollment rate and will allow us to enroll these extra patients within 6 months.

Based on recommendations of our DSMB we decided to increase our enrollment goal and we met our revised enrollment goal with 1171 (53% of those eligible) in March of 2018.

2. Specific Aim #2 Compare bacterial species and antibacterial sensitivities of the bacteria in the patients who develop surgical site infections in study patients treated with Supplemental Perioperative Oxygen compared to those treated without Supplemental Perioperative Oxygen.

2.1 Finalize Study Protocol

The general progress and timing of the study protocol creation regarding specific aim #2 are identical to those described in specific aim above in section 1.

2.2 Finalize/Adapt/Test Study Materials

The general progress and timing of the creation of the study materials regarding specific aim #2 are identical to those described in specific aim above in section 1.

2.3 Train Study Coordinators

Identical to specific aims #1 as described above in section 1.

2.4 IRB Approval at First Site (Milestone #1)

Identical to specific aims #1 as described above in section 1.

2.5 IRB Approval at All Sites

Identical to specific aims #1 as described above in section 1.

2.6 Enroll First Patient (Milestone #2)

Identical to specific aims #1 as described above in section 1.

2.7 Enrollment

Identical to specific aims #1 as described above in section 1.

3. Specific Aim #3 Validate the previously developed risk prediction model for the development of surgical site infections after fracture surgery (Reference 2,3,4,5).

3.1 Interim Analysis/Final Analysis

One of the specific aims of this project is to validate a model to predict risk for infection after orthopaedic fracture surgery. We are basing this off our previous work and have done an analysis of our pilot data (different treatment but similar patient population [1]) to analyze risk factors for infection. This has now been published in J Trauma [2,3,4,5].

This work can only begin after patient follow up has been completed.

4. Specific Aim #4 Measure and compare resource utilization and cost associated with surgical site infection in study patients treated with Supplemental Perioperative Oxygen compared to those treated without Supplemental Perioperative Oxygen

4.1 Interim Analysis/Final Analysis

One of the specific aims of this project is to evaluate this technique in terms of cost. Determining the "cost effectiveness" of this technique will be important in determining if it is appropriate for broader distribution. Our hypothesis is that it is such a low cost technique that even modest decreases in infection rate will be very cost effective.

This work can only begin after patient enrollment and follow up has been completed. We have completed enrollment of 1171 patients and one year follow up will be completed this spring.

4. KEY RESEARCH ACCOMPLISHMENTS:

Our key research accomplishments during year six of the grant include:

1. 29 study sites enrolled at least 1 patient.
2. Revised goal of 1171 patients all enrolled (March 2018)
3. 738 patients have completed the study to date.
4. 88% follow-up rate at 12 month follow up.
5. Study is on pace to complete patient follow-up in a reasonable time frame.

5. CONCLUSION

We believe that this project has significant potential to impact wounded warriors' and civilians' outcomes by reducing the rate of surgical site infection if our primary hypothesis is confirmed.

This past year demonstrates that we are clearly on track for study success. We have completed enrolling patients (n=1171) and have a high follow up rate. There are no barriers to study success and we look forward to finishing the study off study follow up in the spring of 2019.

6. PUBLICATION, ABSTRATS, AND PRESENTATIONS

Protocol paper published.

7. INVENTIONS, PATENST, AND LICENSES

Nothing to report

8. REPORTABLE OUTCOMES

Nothing to report

9. OTHER ACHEIVEMENTS

Nothing to report

10. REFERENCES:

1. Stall A, Paryavi E, Gupta R, Zadnik M, Hui E, O'Toole RV, "Perioperative supplemental oxygen to reduce surgical site infection after open fixation of high-risk fractures: A randomized controlled pilot trial" J Trauma Acute Care Surg 2013 Volume 75 Number 4 657-63.

2. Paryavi E, Stall A, Gupta R, Zadnik M, Hui E, Castillo RC, Scharfstein DO, O'Toole RV "A Predictive Model for Perioperative Assessment of Infection Risk in High Energy Lower Extremity Injuries" Podium Presentation at American Academy of Orthopaedic Surgeons, San Diego, CA, 2011.

3. Paryavi E, Stall A, Gupta R, Zadnik M, Hui E, Castillo RC, Scharfstein DO, O'Toole RV "A Predictive Model for Perioperative Assessment of Infection Risk After Surgery for High Energy Lower Extremity Injuries: Development of the Risk of Infection in Orthopaedic Trauma Surgery (RIOTS) Score" Podium Presentation at OREF Chesapeake Region Resident Research Symposium, December 2010.

4. Paryavi E, Stall A, Gupta R, Zadnik M, Hui E, Castillo RC, Scharfstein DO, O'Toole RV "A Predictive Model for Perioperative Assessment of Infection Risk in High Energy Lower Extremity Injuries" Poster Presentation 26th Annual Meeting of Orthopaedic Trauma Association, Baltimore, MD, October 2010.

5. Paravi E, Stall A, Gupta R, Scharfstein DO, Castillo RC, Zadnik M, Hui E, O'Toole RV, "Predictive model for surgical site infection risk after surgery for high-energy lower extremity fractures: Development of the Risk of Infection in Orthopedic Trauma Surgery Score" J Trauma Acute Care Surg 2013 Volume 74 Number 6 1521-27.

6. O'Toole RV, Joshi M, Carlini AR, Sikorski RA, Dagal A, Murray CK, Weaver MJ, Paryavi E, Stall AC, Scharfstein DO, Agel J, Zadnik M, Bosse MJ, Castillo RC, METRC "Supplemental Perioperative Oxygen to Reduce Surgical Site INfeciton Afer High-Energy Fracture Surgery (OXYGEN Study) J Orthop Trauma 2017 Apr;31 Suppl 1: S25-S31.

11. APPENDICES:

Appendix 1. Protocol Committee

First Name	Last Name	Role	Site	
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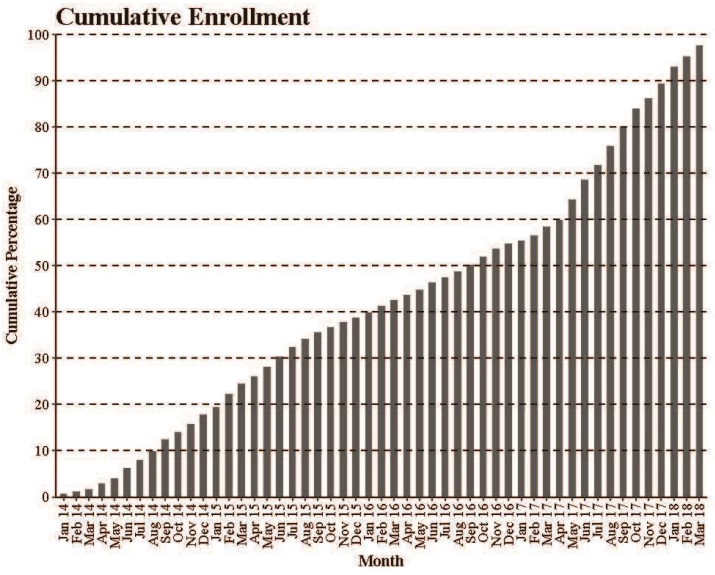
Appendix 2. Oxygen Monthly Report (Oct 1, 2018)

OXYGEN Monthly Report

Supplemental Oxygen to Reduce Surgical Site Infection

Data as of October 1, 2018



Enrollment Updates

- There are 27 centers participating in this study (all centers are certified).
- 4354 patients have been screened for eligibility and of these, 2312 (53%) were eligible.
- 1171 (51% of eligible) were consented and enrolled.
- We have now reached 98% of our total enrollment goal (see figure)
- 738 patients have completed the study.

Screening and Enrollment Summary
All Participating Sites

Facility	Days Certified	Expected Screened	Number Screened	Number Enrolled	Enrolled This Month	Completed	Discontinued
ALL			4354	1171	0	738	96
UWA	1385	1073	528	212	0	164	17
UMD	1746	1062	691	189	0	138	2
HOU	1680	585	393	138	0	77	16
CMC	1697	590	652	131	0	82	4
HRV	1484	-	172	79	0	56	13
MTH	1494	577	339	59	0	41	3
VMC	1573	526	299	58	0	37	2
AGY	1544	-	70	33	0	26	7
LUB	476	-	27	27	0	0	5
ESK	1475	-	123	25	0	17	2
UKY	410	-	26	24	0	0	0
BMC	1554	332	123	22	0	17	4
USF	1519	308	71	18	0	3	1
MIN [1]	812	138	63	18	0	18	0
MET	462	151	97	17	0	0	1
YRK	1515	-	20	17	0	13	3
UOK	1400	245	88	15	0	8	3
PEN	1440	-	43	15	0	6	7
NSD	1537	51	14	13	0	7	0
UWI	343	-	13	11	0	0	2
SPC [2]	902	227	77	10	0	9	1
COR	759	-	65	10	0	10	0
DAR	459	-	8	8	0	0	0
WFU	1670	686	243	7	0	7	0
CED	371	-	7	6	0	0	1
CAM	1032	-	80	3	0	2	1
STN	602	-	4	3	0	0	1
PSU	472	107	14	2	0	0	0

Facility	Days Certified	Expected Screened	Number Screened	Number Enrolled	Enrolled This Month	Completed	Discontinued
HAC	420	-	4	1	0	0	0

[1] MIN is a dual site comprised of HCM and UMN, however only HCM was participating in this study. HCM withdrew from participating after becoming certified.
[2] SPC withdrew from participating after becoming certified.

Questions? Study Contacts:

- Study PI: Robert O'Toole, MD (ROtoole@umoa.umm.edu)
- MCC PI: Renan Castillo, PhD (rcastil1@jhu.edu)
- MCC Project Director: Anthony R. Carlini, MS (acarlini@jhu.edu)
- MCC Study Manager: Susan Collins, MSc (scollins@jhsph.edu)

Monthly Table 1
Number of Subjects Screened [3], Eligible, Enrolled, and Not Enrolled
Cumulative by Site

Facility	Days Certified [4]	Expected Screened	Number Screened	Number Eligible	Among those Eligible (% Eligible)		
					Number Enrolled	Number Refused	Number Not Enrolled
ALL			4354	2312 (53%)	1171 (51%)	312 (13%)	829 (36%)
AGY	1544	-	70	41 (59%)	33 (80%)	5 (12%)	3 (7%)
BMC	1554	332	123	30 (24%)	22 (73%)	3 (10%)	5 (17%)
CAM	1032	-	80	64 (80%)	3 (5%)	14 (22%)	47 (73%)
CED	371	-	7	7 (100%)	6 (86%)	0 (0%)	1 (14%)
CMC	1697	590	652	396 (61%)	131 (33%)	74 (19%)	191 (48%)
COR	759	-	65	30 (46%)	10 (33%)	3 (10%)	17 (57%)
DAR	459	-	8	8 (100%)	8 (100%)	0 (0%)	0 (0%)
ESK	1475	-	123	45 (37%)	25 (56%)	20 (44%)	0 (0%)
HAC	420	-	4	4 (100%)	1 (25%)	0 (0%)	3 (75%)
HOU	1680	585	393	209 (53%)	138 (66%)	32 (15%)	39 (19%)
HRV	1484	-	172	142 (83%)	79 (56%)	47 (33%)	16 (11%)
LUB	476	-	27	27 (100%)	27 (100%)	0 (0%)	0 (0%)
MET	462	151	97	34 (35%)	17 (50%)	6 (18%)	11 (32%)
MIN	WFS	138	63	28 (44%)	18 (64%)	1 (4%)	9 (32%)
MTH	1494	577	339	111 (33%)	59 (53%)	9 (8%)	43 (39%)
NSD	1537	51	14	13 (93%)	13 (100%)	0 (0%)	0 (0%)
PEN	1440	-	43	27 (63%)	15 (56%)	8 (30%)	4 (15%)
PSU	472	107	14	11 (79%)	2 (18%)	1 (9%)	8 (73%)
SPC	WFS	227	77	20 (26%)	10 (50%)	4 (20%)	6 (30%)
STN	602	-	4	4 (100%)	3 (75%)	0 (0%)	1 (25%)
UKY	410	-	26	24 (92%)	24 (100%)	0 (0%)	0 (0%)
UMD	1746	1062	691	415 (60%)	189 (46%)	36 (9%)	190 (46%)
UOK	1400	245	88	42 (48%)	15 (36%)	12 (29%)	15 (36%)
USF	1519	308	71	21 (30%)	18 (86%)	3 (14%)	0 (0%)
UWA	1385	1073	528	351 (66%)	212 (60%)	21 (6%)	118 (34%)
UWI	343	-	13	13 (100%)	11 (85%)	1 (8%)	1 (8%)
VMC	1573	526	299	89 (30%)	58 (65%)	7 (8%)	24 (27%)
WFU	1670	686	243	86 (35%)	7 (8%)	4 (5%)	75 (87%)

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Facility	Days Certified [4]	Expected Screened	Number Screened	Number Eligible	Among those Eligible (% Eligible)		
					Number Enrolled	Number Refused	Number Not Enrolled
YRK	1515	-	20	20 (100%)	17 (85%)	1 (5%)	2 (10%)

[3] Number screened based on all patients with completed CRF00
[4] WFS = Withdrawn From Study (post-certification)

Monthly Table 2

Number of Subjects Enrolled/Screened by Month of Participation and Site (past 24 months only)

Month	ALL	UMD	CMC	HOU	WFU	VMC	BMC	AGY	NSD	USF	YRK	MTH	HRV	ESK	PEN	UOK	UWA	CAM	SPC	HCM
Sep 2016	17/126	1/29	1/22	1/1	0/7	0/6	2/6	2/4	0/0	0/0	0/0	0/7	2/6	1/6	0/0	0/0	4/13	2/13	0/0	–
Oct 2016	20/119	1/18	2/20	0/1	0/10	0/11	0/3	1/2	0/0	1/1	0/0	0/11	2/5	1/2	0/0	0/2	12/25	0/3	0/0	–
Nov 2016	22/107	3/17	1/17	3/6	0/8	0/10	2/4	0/1	0/0	2/3	0/0	1/6	4/6	0/5	1/1	0/1	5/11	0/5	WFS	–
Dec 2016	13/87	1/13	1/22	1/3	0/0	0/9	0/1	0/0	1/1	1/3	0/0	0/7	2/3	1/4	0/0	0/0	4/12	0/1	–	–
Jan 2017	7/75	0/18	0/8	1/1	0/9	0/11	0/4	0/0	0/0	0/0	0/0	0/8	0/2	0/2	0/0	0/0	5/9	0/2	–	–
Feb 2017	14/83	0/10	0/19	5/10	0/2	0/5	0/2	1/1	0/0	1/6	0/0	0/3	1/3	0/1	0/1	1/1	5/12	0/3	–	–
Mar 2017	22/92	3/7	0/16	6/10	0/10	0/5	1/2	0/0	0/0	0/1	0/0	0/3	3/5	0/4	0/0	0/0	9/13	0/5	–	–
Apr 2017	18/101	1/16	2/15	6/13	0/0	0/17	0/3	0/1	0/0	1/4	0/0	0/3	1/4	0/4	0/0	0/0	6/10	0/1	–	–
May 2017	52/134	8/24	11/18	8/16	0/0	4/27	0/1	0/0	0/0	0/2	0/0	8/16	0/5	1/4	0/0	0/3	10/15	0/0	–	–
Jun 2017	53/130	8/20	8/19	8/20	0/0	3/14	0/2	0/0	2/2	0/1	0/0	4/16	2/4	1/4	1/1	1/5	13/19	0/0	–	–
Jul 2017	37/105	5/17	8/12	4/14	0/0	2/12	0/1	0/0	0/0	1/3	0/0	7/15	1/7	0/4	0/0	1/6	4/5	0/0	–	–
Aug 2017	50/130	9/19	8/21	2/8	0/0	2/14	0/5	0/0	0/0	0/2	0/0	4/8	0/2	1/5	0/0	0/4	14/15	0/0	–	–
Sep 2017	52/160	13/20	4/10	8/11	0/0	5/15	0/5	0/1	2/2	1/2	0/0	1/13	1/5	1/4	1/1	0/4	3/49	0/0	–	–
Oct 2017	45/91	7/10	10/19	7/13	0/0	0/0	1/2	0/0	0/0	0/0	0/0	2/6	1/5	1/1	0/0	0/3	2/8	0/0	–	–
Nov 2017	27/88	0/0	4/13	7/12	0/0	1/15	0/0	0/0	0/0	0/0	0/0	1/10	1/5	0/3	0/0	0/0	1/2	0/0	–	–
Dec 2017	38/94	6/10	5/12	6/10	0/0	0/12	0/0	0/0	1/1	0/0	0/0	3/10	0/0	0/0	0/0	0/3	2/10	0/0	–	–
Jan 2018	44/116	8/20	5/15	6/14	0/0	3/12	0/0	0/0	1/1	0/1	0/0	0/5	3/4	1/3	0/0	1/1	1/11	0/0	–	–
Feb 2018	25/84	2/10	5/10	2/14	0/0	0/7	0/0	0/0	0/0	0/1	0/0	0/0	0/3	0/2	0/0	0/4	5/10	0/0	–	–
Mar 2018	30/94	4/15	2/5	7/16	0/0	0/8	0/0	0/0	0/0	0/3	0/0	2/2	2/5	1/3	0/0	1/4	3/9	0/0	–	–
Apr 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	–	–
May 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	–	–
Jun 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	–	–
Jul 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	–	–
Aug 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	–	–
Sep 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	–	–

Month	ALL	COR	STN	LUB	PSU	MET	DAR	HAC	UKY	CED	UWI	COL	MCR
Sep 2016	17/126	1/6											
Oct 2016	20/119	0/5											
Nov 2016	22/107	0/6											
Dec 2016	13/87	1/8											
Jan 2017	7/75	1/1											
Feb 2017	14/83	0/4	0/0										
Mar 2017	22/92	0/10	0/1										
Apr 2017	18/101	1/10	0/0										
May 2017	52/134	1/2	1/1										
Jun 2017	53/130	2/3	0/0	0/0	0/0	0/0	0/0						
Jul 2017	37/105	2/5	0/0	1/1	0/0	1/3	0/0						
Aug 2017	50/130	1/4	0/0	3/3	0/0	2/16	2/2	0/0	2/2				
Sep 2017	52/160	0/0	0/0	5/5	0/1	0/4	0/0	1/1	6/7	0/0			
Oct 2017	45/91	0/0	0/0	4/4	0/0	2/11	4/4	0/0	3/3	1/2	0/0	0/0	0/0
Nov 2017	27/88	0/1	1/1	2/2	0/1	2/14	2/2	0/0	2/3	0/0	3/4	0/0	0/0
Dec 2017	38/94	0/0	0/0	2/2	1/2	3/12	0/0	0/1	4/4	4/4	1/1	0/0	0/0
Jan 2018	44/116	0/0	0/0	5/5	0/4	3/11	0/0	0/2	2/2	1/1	4/4	0/0	0/0
Feb 2018	25/84	0/0	1/1	1/1	1/4	2/10	0/0	0/0	3/3	0/0	3/4	0/0	0/0
Mar 2018	30/94	0/0	0/0	4/4	0/2	2/16	0/0	0/0	2/2	0/0	0/0	0/0	0/0
Apr 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
May 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Jun 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Jul 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Aug 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Sep 2018	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

Monthly Table 3
Number of Expected [5], Completed [6], and Missed [7] Visits by Study Visit
E = Expected, C = Completed, M = Missed

Facility	Enrolled	2 week			3 month			6 month			12 month			Overall		
		E	C	M	E	C	M	E	C	M	E	C	M	E	C	M
ALL	1171	1130	1124 (99%)	3 (0%)	1124	1054 (94%)	50 (4%)	1097	960 (88%)	71 (6%)	869	769 (88%)	26 (3%)	4220	3907 (93%)	150 (4%)
AGY	33	33	33 (100%)	0 (0%)	33	30 (91%)	3 (9%)	31	27 (87%)	4 (13%)	28	26 (93%)	2 (7%)	125	116 (93%)	9 (7%)
BMC	22	20	20 (100%)	0 (0%)	19	19 (100%)	0 (0%)	20	19 (95%)	1 (5%)	18	17 (94%)	1 (6%)	77	75 (97%)	2 (3%)
CAM	3	3	3 (100%)	0 (0%)	3	2 (67%)	1 (33%)	3	2 (67%)	1 (33%)	2	2 (100%)	0 (0%)	11	9 (82%)	2 (18%)
CED	6	5	5 (100%)	0 (0%)	5	3 (60%)	0 (0%)	5	0 (0%)	0 (0%)	0	0 (0%)	0 (0%)	15	8 (53%)	0 (0%)
CMC	131	131	131 (100%)	0 (0%)	130	127 (98%)	2 (2%)	128	121 (95%)	2 (2%)	99	88 (89%)	1 (1%)	488	467 (96%)	5 (1%)
COR	10	10	10 (100%)	0 (0%)	10	10 (100%)	0 (0%)	10	10 (100%)	0 (0%)	10	10 (100%)	0 (0%)	40	40 (100%)	0 (0%)
DAR	8	8	8 (100%)	0 (0%)	8	8 (100%)	0 (0%)	8	7 (88%)	0 (0%)	2	2 (100%)	0 (0%)	26	25 (96%)	0 (0%)
ESK	25	25	25 (100%)	0 (0%)	25	20 (80%)	4 (16%)	25	22 (88%)	2 (8%)	21	17 (81%)	2 (10%)	96	84 (88%)	8 (8%)
HAC	1	1	1 (100%)	0 (0%)	1	1 (100%)	0 (0%)	1	1 (100%)	0 (0%)	0	0 (0%)	0 (0%)	3	3 (100%)	0 (0%)
MIN	18	18	18 (100%)	0 (0%)	18	18 (100%)	0 (0%)	18	15 (83%)	3 (17%)	18	18 (100%)	0 (0%)	72	69 (96%)	3 (4%)
HOU	138	134	133 (99%)	1 (1%)	133	118 (89%)	14 (11%)	127	106 (83%)	9 (7%)	91	82 (90%)	3 (3%)	485	439 (91%)	27 (6%)
HRV	79	75	75 (100%)	0 (0%)	73	70 (96%)	3 (4%)	71	68 (96%)	3 (4%)	63	59 (94%)	1 (2%)	282	272 (96%)	7 (2%)
LUB	27	23	23 (100%)	0 (0%)	23	22 (96%)	1 (4%)	22	16 (73%)	0 (0%)	5	5 (100%)	0 (0%)	73	66 (90%)	1 (1%)
MET	17	16	16 (100%)	0 (0%)	16	15 (94%)	0 (0%)	15	11 (73%)	0 (0%)	3	3 (100%)	0 (0%)	50	45 (90%)	0 (0%)
MTH	59	56	56 (100%)	0 (0%)	56	55 (98%)	0 (0%)	55	51 (93%)	2 (4%)	48	41 (85%)	0 (0%)	215	203 (94%)	2 (1%)
NSD	13	13	13 (100%)	0 (0%)	13	12 (92%)	0 (0%)	13	13 (100%)	0 (0%)	9	9 (100%)	1 (11%)	48	47 (98%)	1 (2%)
PEN	15	14	12 (86%)	1 (7%)	14	12 (86%)	1 (7%)	10	9 (90%)	1 (10%)	8	6 (75%)	2 (25%)	46	39 (85%)	5 (11%)
PSU	2	2	1 (50%)	0 (0%)	2	2 (100%)	0 (0%)	2	2 (100%)	0 (0%)	0	0 (0%)	0 (0%)	6	5 (83%)	0 (0%)
SPC	10	10	10 (100%)	0 (0%)	10	10 (100%)	0 (0%)	10	10 (100%)	0 (0%)	9	9 (100%)	0 (0%)	39	39 (100%)	0 (0%)
STN	3	3	3 (100%)	0 (0%)	2	2 (100%)	0 (0%)	2	2 (100%)	0 (0%)	1	1 (100%)	0 (0%)	8	8 (100%)	0 (0%)
UKY	24	24	24 (100%)	0 (0%)	24	19 (79%)	0 (0%)	22	12 (55%)	0 (0%)	3	0 (0%)	0 (0%)	73	55 (75%)	0 (0%)
UMD	189	188	188 (100%)	0 (0%)	188	181 (96%)	6 (3%)	185	165 (89%)	18 (10%)	152	140 (92%)	1 (1%)	713	674 (95%)	25 (4%)
UOK	15	13	13 (100%)	0 (0%)	13	13 (100%)	0 (0%)	12	11 (92%)	1 (8%)	10	9 (90%)	1 (10%)	48	46 (96%)	2 (4%)

[5] A visit is counted as complete (i.e. fully or partially completed) if at least one field in the CRFs to be completed for the visit has been keyed and this visit has not been indicated as missed on AF03. All out of window visits count as completed for the purpose of this report.

[6] A visit is counted as expected when the visit has been completed (as defined above) or when the visit window has been closed for 7 days and no forms have been keyed. Patients who withdraw/ are lost to follow up are kept in as incomplete visits. Deaths are censored at time of death. Patients inappropriately enrolled are removed from all totals. Patients for whom Time Zero (e.g. date of injury) is incomplete are excluded from this report.

[7] A visit is counted as missed based on AF03. Patients with no AF03 or no data entered into REDCap will be listed in Query 2.

Facility	Enrolled	2 week			3 month			6 month			12 month			Overall		
		E	C	M	E	C	M	E	C	M	E	C	M	E	C	M
USF	18	17	15 (88%)	1 (6%)	17	12 (71%)	3 (18%)	17	8 (47%)	7 (41%)	16	7 (44%)	2 (12%)	67	42 (63%)	13 (19%)
UWA	212	200	200 (100%)	0 (0%)	200	189 (94%)	9 (4%)	197	177 (90%)	14 (7%)	183	161 (88%)	8 (4%)	780	727 (93%)	31 (4%)
UWI	11	9	9 (100%)	0 (0%)	9	9 (100%)	0 (0%)	10	8 (80%)	0 (0%)	0	0 (0%)	0 (0%)	28	26 (93%)	0 (0%)
VMC	58	56	56 (100%)	0 (0%)	56	53 (95%)	2 (4%)	55	45 (82%)	2 (4%)	49	37 (76%)	0 (0%)	216	191 (88%)	4 (2%)
WFU	7	7	7 (100%)	0 (0%)	7	6 (86%)	1 (14%)	7	7 (100%)	0 (0%)	7	7 (100%)	0 (0%)	28	27 (96%)	1 (4%)
YRK	17	16	16 (100%)	0 (0%)	16	16 (100%)	0 (0%)	16	15 (94%)	1 (6%)	14	13 (93%)	1 (7%)	62	60 (97%)	2 (3%)

Monthly Table 4
Evaluate Oxygen treatment adherence by Site [8]
By Average Absolute Deviation [9], % Observations Within Range 1 [10] and % Observations Within Range 2 [11]

Facility	Data	Average Absolute Deviation			% of Observations within Range 1			% Observations within Range 2		
		Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range
ALL	1057	7.2 ± 10.0	4.1	(0.0, 71.8)	78.2 ± 30.9	90.9	(0.0, 100.0)	84.1 ± 27.7	97.7	(0.0, 100.0)
UWA	195	5.6 ± 8.0	3.5	(0.0, 49.4)	84.8 ± 23.3	93.3	(0.0, 100.0)	87.8 ± 22.0	95.5	(0.0, 100.0)
UMD	184	8.3 ± 11.6	5.2	(0.0, 64.0)	78.8 ± 34.8	94.9	(0.0, 100.0)	82.1 ± 32.5	100.0	(0.0, 100.0)
CMC	127	9.0 ± 8.4	6.3	(0.0, 36.2)	71.1 ± 28.1	80.0	(0.0, 100.0)	81.4 ± 26.1	91.0	(0.0, 100.0)
HOU	122	4.6 ± 6.3	3.0	(0.0, 39.9)	81.9 ± 26.4	92.1	(0.0, 100.0)	87.5 ± 24.6	100.0	(0.0, 100.0)
HRV	66	4.9 ± 6.6	2.7	(0.4, 37.4)	82.2 ± 25.4	92.3	(0.0, 100.0)	86.1 ± 24.9	100.0	(0.0, 100.0)
MTH	56	8.1 ± 12.1	4.1	(0.0, 61.4)	68.2 ± 39.7	90.0	(0.0, 100.0)	82.1 ± 31.2	100.0	(0.0, 100.0)
VMC	52	10.7 ± 14.5	5.7	(0.0, 56.0)	64.8 ± 35.7	80.6	(0.0, 100.0)	75.7 ± 32.4	88.6	(0.0, 100.0)
AGY	26	7.7 ± 12.0	2.4	(0.0, 42.8)	76.4 ± 33.6	93.0	(0.0, 100.0)	79.2 ± 33.9	96.9	(0.0, 100.0)
ESK	23	4.9 ± 7.2	1.1	(0.0, 26.6)	84.6 ± 30.2	100.0	(0.0, 100.0)	91.5 ± 21.6	100.0	(0.0, 100.0)
LUB	22	9.2 ± 16.3	2.1	(0.0, 71.8)	71.8 ± 40.0	93.3	(0.0, 100.0)	83.3 ± 32.8	100.0	(0.0, 100.0)
UKY	22	4.7 ± 9.0	1.5	(0.0, 39.3)	87.7 ± 25.8	96.5	(0.0, 100.0)	88.6 ± 24.8	100.0	(0.0, 100.0)
BMC	18	3.9 ± 4.3	2.5	(0.6, 16.7)	91.8 ± 10.8	93.2	(57.1, 100.0)	93.3 ± 10.8	100.0	(57.1, 100.0)
HCM	18	4.9 ± 3.0	4.3	(1.2, 11.9)	90.6 ± 23.7	100.0	(0.0, 100.0)	91.5 ± 23.9	100.0	(0.0, 100.0)
USF	17	3.9 ± 3.1	2.6	(0.9, 10.7)	86.9 ± 13.8	94.1	(56.2, 100.0)	90.2 ± 14.2	97.4	(56.2, 100.0)
YRK	14	6.6 ± 5.9	4.5	(1.5, 18.2)	73.5 ± 40.3	97.6	(0.0, 100.0)	88.9 ± 24.8	100.0	(12.5, 100.0)
NSD	13	17.8 ± 17.9	7.5	(0.0, 52.9)	53.6 ± 40.3	73.3	(0.0, 100.0)	57.3 ± 43.4	86.7	(0.0, 100.0)

[8] This table describes adherence to the randomized oxygen concentrations (80% or 80% FiO_2). To preserve blinding, sites with at least 5 patients enrolled are included on this table. There are three sets of means, medians, and ranges in the table. They represent:

[9] Average Absolute Deviation: This set of mean, median, and range measures the distance of each observation recorded on CRF15 from either 80% or 80%, depending on which group the patient was randomized to, and excluding the 1st and last observations recorded. The mean shown here is a mean of the means, and the median is the median of several means. A higher median in this cluster indicates "worse" protocol adherence.

[10] % Observations Within Range 1: This set of mean, median, and range measures the percent of observations recorded on CRF15 that fall within either $20-85\%$ or $70-85\%$, depending on which group the patient was randomized to, and excluding the 1st and last observations recorded. This is our more stringent definition of protocol adherence. A higher median in this cluster indicates "better" protocol adherence.

[11] % of Observations Within Range 2: This set of mean, median, and range measures the percent of observations recorded on CRF15 that are $< 85\%$ or $> 70\%$, depending on which group the patient was randomized to, and excluding the 1st and last observations recorded. This is our more lenient definition of protocol adherence. A higher median in this cluster indicates "better" protocol adherence.

Table 4 (con't)

Facility	Data	Average Absolute Deviation			% of Observations within Range 1			% Observations within Range 2		
		Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range
UOK	12	5.6 ± 2.7	5.9	(1.3, 11.0)	92.1 ± 12.2	98.4	(62.5, 100.0)	94.6 ± 9.7	100.0	(75.0, 100.0)
MET	11	17.1 ± 10.0	15.1	(5.2, 33.2)	31.6 ± 35.7	9.5	(0.0, 83.3)	49.1 ± 43.8	62.5	(0.0, 100.0)
COR	10	11.0 ± 21.4	4.6	(0.0, 70.0)	64.0 ± 40.6	76.7	(0.0, 100.0)	75.6 ± 35.9	100.0	(0.0, 100.0)
SPC	9	3.3 ± 3.8	1.2	(0.3, 10.9)	95.7 ± 6.8	100.0	(83.3, 100.0)	96.1 ± 6.7	100.0	(83.3, 100.0)
UWI	9	6.7 ± 6.8	5.1	(1.1, 24.3)	85.4 ± 32.5	98.2	(0.0, 100.0)	85.6 ± 32.6	100.0	(0.0, 100.0)
DAR	8	6.0 ± 4.3	5.1	(1.9, 14.4)	64.8 ± 34.9	70.8	(0.0, 100.0)	92.5 ± 13.2	100.0	(62.5, 100.0)
PEN	8	7.7 ± 9.6	3.4	(0.9, 26.2)	78.5 ± 34.2	90.2	(0.0, 100.0)	89.2 ± 14.5	96.4	(62.5, 100.0)
WFU	7	10.4 ± 9.0	7.1	(1.1, 23.5)	71.8 ± 26.1	77.8	(23.1, 100.0)	75.8 ± 28.0	80.0	(23.1, 100.0)

Supplemental Perioperative Oxygen to Reduce Surgical Site Infection After High Energy Fracture Surgery

OR110123 (W81XWH-12-1-0588)

PI: Robert V. O'Toole, MD **Org:** Department of Orthopaedic Surgery, Univ of Maryland **Award Amount:** $2.64M (Directs only)

Study/Product Aim(s)

Our hypothesis is that the use of supplemental perioperative oxygen for fractures at high risk for infection will reduce infection rates and therefore improve outcomes compared to treatment without this technique.

- **Infection rates will be lower in the treatment arm**
- **There will be no difference in bacterial susceptibilities in the treatment arm**
- **Validate our previous RIOTS model that predicts infection**

Approach

The study uses the DOD-funded METRC infrastructure for a multicenter randomized controlled treatment trial. The study population is patients with high energy tibial plateau, pilon (distal tibia), and calcaneus fractures. The study is guided by a pilot study already completed of 250 fractures at our center. We plan to enroll 1000 patients.

Surgical Site infection (left) in orthopaedic trauma is thought to be affected by biofilm formation (Right). General surgery clinical literature suggests that supplemental perioperative oxygen might limit surgical site infection. The effect on orthopaedic trauma surgery awaits the outcome of this trial.

Accomplishment: We finalized the protocol, CRFs, study sites, and have IRB approval and site certification at 29 sites. 1171 patients have been enrolled with f/u rate of 88% at 1 year. Follow up should be complete this spring.

Timeline and Cost

Activities CY	13	14	15/16	17/18/19
Develop and Approve Protocol				
IRB approval at Multiple sites				
Enroll/Follow Patients				
Analysis				
Estimated Budget ($K)	$ 165,127	$741,645	$1,741,138	$0

Updated: (10/29/2018)

Goals/Milestones

Year 1: CY13-14 Goal –Protocol Development/Implementation/IRB

☑ Develop protocol and gain approval of METRC steering committee
☑ IRB approval at METRC Coordinating center and DOD
☑ IRB approval at PI site
☑ Perform site education program for research coordinators
☑ Develop site educational and study materials

Year 2: CY14-15 Goals – Patient enrollment

☑ Begin patient enrollment
☑ IRB/DOD approval at all study sites (24/25 completed to date)

Year 3: CY14-17 Goals – Enrollment completion

☐ Complete patient enrollment & study analysis

Comments/Challenges/Issues/Concerns

- Patient enrollment is >12 months behind due to IRB delays.

Budget Expenditure to Date

Projected Expenditure: $270,250 (including JHU sub payments)
Actual Expenditure: $2,377,660 (including JHU sub payment)