

AWARD NUMBER: W81XWH-17-1-0532

TITLE: Multicenter Randomized Trial of Everolimus in Pediatric Heart Transplantation

PRINCIPAL INVESTIGATOR: Sleeper, Lynn A.

CONTRACTING ORGANIZATION: Boston Children's Hospital
Boston, MA 02115

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14. ABSTRACT TEAMMATE is a multicenter randomized clinical trial of a novel immunosuppressive therapy that will study 210 children who have undergone recent heart transplantation. The primary goal is to determine whether a new rejection treatment (everolimus and low-dose tacrolimus) can reduce or prevent complications of transplant, including rejection, coronary artery disease, and kidney disease, when compared to usual care (tacrolimus and mycophenolate mofetil). The secondary goal is to acquire FDA approval of the first immunosuppression regimen for pediatric heart transplantation. The primary trial endpoint is a validated surrogate measure—the major adverse transplant event (MATE) score—which efficiently predicts long-term survival, and that has been accepted by the FDA (IND# 127980). The trial is being conducted at 26 centers, with leadership at Boston Children's Hospital (Data Coordinating Center) and Stanford University (Clinical Coordinating Center). At the time of this annual report, 25 of 26 centers are fully initiated and able to screen and enroll patients. A total of 151 patients have been randomized (108 in the last year). Additional accomplishments in Year 02 include one in-person Protocol Certification Trainings; the addition of two study sites; successful execution of two Data and Safety Monitoring Board meetings and an in-person Steering Committee meeting; acceptance of a research abstract on everolimus dosing; and creation of a Spanish language informed consent video for families, and the commencement of regulatory/data audit site visits.						
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TEAMMATE is a multicenter randomized clinical trial of a novel immunosuppressive therapy that will study 210 children who have undergone recent heart transplantation. The primary goal is to determine whether a new rejection treatment (everolimus and low-dose tacrolimus) can reduce or prevent complications of transplant, including rejection, coronary artery disease, and kidney disease, when compared to usual care (tacrolimus and mycophenolate mofetil). The secondary goal is to acquire FDA approval of the first immunosuppression regimen for pediatric heart transplantation. The primary trial endpoint is a validated surrogate measure—the major adverse transplant event (MATE) score—which efficiently predicts long-term survival, and that has been accepted by the FDA (IND# 127980). The trial is being conducted at 26 centers, with leadership at Boston Children's Hospital (Data Coordinating Center) and Stanford University (Clinical Coordinating Center). At the time of this annual report, 25 of 26 centers are fully initiated and able to screen and enroll patients. A total of 151 patients have been randomized (108 in the last year). Additional accomplishments in Year 02 include one in-person Protocol Certification Trainings; the addition of two study sites; successful execution of two Data and Safety Monitoring Board meetings and an in-person Steering Committee meeting; acceptance of a research abstract on everolimus dosing; and creation of a Spanish language informed consent video for families, and the commencement of regulatory/data audit site visits.

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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Median survival after pediatric heart transplantation is only 15 years in the current era, due to the occurrence of late complications after heart transplant, most of which stem from the medications used to suppress the immune system in order to prevent graft rejection. While graft survival has improved significantly with the current standard of care, tacrolimus (TAC) and mycophenolate mofetil (MMF), most of the improvement has come from a reduction in early mortality. Preliminary studies suggest that everolimus in combination with low-dose TAC may prevent rejection, coronary artery disease, and kidney failure more effectively than TAC-MMF. However, these studies are limited by single-center design, inconsistent endpoint definitions and use of historical controls. In contrast to adults, children have a substantially longer *potential* life expectancy in the absence of late transplant complications, making the prevention of such complications an urgent priority for the pediatric heart transplant community

The research that is the subject of this report, the TEAMMATE trial, is a multicenter randomized clinical trial of a novel immunosuppressive therapy that will study 210 children who have undergone recent heart transplantation. The primary goal is to determine whether a new rejection treatment (everolimus and low-dose TAC) can reduce or prevent complications of transplant when compared to usual care (TAC-MMF). The secondary goal is to acquire FDA approval of the first immunosuppression regimen for pediatric heart transplantation. The primary trial endpoint is a validated surrogate measure—the major adverse transplant event (MATE) score—which efficiently predicts long-term survival, and that has been accepted by the FDA (IND# 127980). The trial is being conducted at 25 centers, with leadership at Boston Children’s Hospital (Data Coordinating Center) and Stanford University (Clinical Coordinating Center).

This trial has high military relevance: 1) pediatric heart transplant is most often performed in those with congenital heart disease, which may be more common in military families due to *in utero* exposures such as hazardous chemicals, poor air quality, ground water contamination, and infectious diseases that may be more prevalent when serving abroad; 2) the evaluation of everolimus may have medical applications for treating military injuries that require a vascular composite allograft, such as hand transplantation; and 3) proliferation signal inhibitors (such as everolimus) are uniquely known for their ability to alter healing of human tissues, and therefore may provide insights into mechanistic pathways necessary to expedite wound healing.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Children, heart transplant, immunosuppression, randomized clinical trial, everolimus

3. ACCOMPLISHMENTS:

What were the major goals of the project?

*The **OVERALL AIM** of the research is to execute a multicenter randomized trial enrolling 210 pediatric heart transplant recipients from 26 sites to evaluate the efficacy, safety and tolerability of everolimus+low-dose tacrolimus and to secure its FDA approval.*

Major Tasks per SOW include:

- | | |
|--|-----------------|
| 1. Regulatory & Contractual Activities required for Study Launch | Months -6 to 3 |
| 2. Prepare Study Staff and Systems to Execute Trial | Months 1 to 3 |
| 3. Participant Recruitment | Months 4 to 18 |
| 4. Participant Follow-up and Evaluation | Months 4 to 48 |
| 5. Study Closeout and Analysis | Months 36 to 48 |

Table 1. Statement of Work Tasks and Completion Status

Major Task 1: Regulatory & Contractual Activities required for Study Launch	Timeline (mo)	Status
Subtask 1: Obtain regulatory approvals for study protocol		
Submit final protocol to U.S. FDA for review and approval of amendments to Investigational New Drug (IND) application #127980	-6 to -3	✓ 11/20/17
Submit final protocol for Military IRB (ORP/HRPO) review and approval	-3 to 0	✓ 9/21/17 (v1)
Coordinate with Sites for IRB submission of protocol and ICF	1-3	✓ 27 fully approved
DSMB organizational and protocol review meeting, arranged by DCC	2	✓ 11/01/17
Submit amendments, adverse events and protocol deviations as needed	As Needed	Amendment #17 approved 08/06/2019
Submit annual single IRB report for continuing review	Annually	✓
<i>Milestone Achieved: Approval by Military HRPO and FDA</i>	1	✓

<i>Milestone Achieved: Local IRB approval at Study Sites and Angio Core Laboratory</i>	3	COMPLETE
Subtask 2: Execute financial agreements / subawards		
Coordinate with CCC, 27 Sites (22 original, 5 new, minus 1 terminated = 26 currently) and Core Lab to execute Subcontracts/ CTAs	1-3	✓ All fully executed
Execute Consultant Agreements with Adjudication Committee members	1-3	✓
<i>Milestone Achieved: All Subcontracts and Consultant Agreements executed</i>	1-3	COMPLETE
Major Task 2: Prepare Study Staff and Systems to Execute Trial		
Subtask 1: Training of Research Staff		
DCC/CCC to conduct in-person training session for certification on study protocol	2-3	✓ 11/10/17 in Anaheim, CA; 7/19/18 in Palo Alto, CA 1/11/19 in Boston, MA
DCC/CCC to conduct webinars for SCs to review study protocol procedures	2-3	✓ (occurs monthly)
Angio Core Lab to conduct webinar with site angiographers and site study coordinators regarding data transfer and image acquisition	3	✓ (held 2/1/18)
Adjudication Committee webinar to standardize AE review procedures	3	✓ (calls held Jan, Feb, April, May 2018)
Retrain site study coordinators/Train new coordinators as needed via Webinar	As Needed	✓ 72 Study & Transplant Coords + 33 PIs trained

<i>Milestone Achieved: Research staff trained</i>	3	COMPLETE
Subtask 2: Build Trial materials and communications and database system		
Finalize case report forms, including pilot testing with core site SCs	1-3	✓ 53 CRFs finalized
Create Trial and Angio Core Lab Manuals of Operation (MOO)	2-3	✓
Develop Administrative website to post trial materials and secure documents	1-3	✓
Develop and test database management and randomization systems	2-3	✓ 53 of 53 CRFs in use (100%)
Angio Core Lab to obtain license from Ambra Health for secure image transfer	1	✓ 12/14/17
<i>Milestone Achieved: Study systems developed and functional for trial launch</i>	3	COMPLETE
Major Task 3: Participant Recruitment		
Site Study Coordinators screen records for eligibility and randomize consented patients; CCC on call for eligibility questions from sites	4-18	440 screened 151 of target 210 randomized
Teleconference with SCs every other week and site PIs monthly	4-18	✓
<i>Milestone Achieved: Recruitment and randomization of 210 participants</i>	18	CONTINUING
Major Task 4: Participant Follow-up and Evaluation (0,3,6,9,12,18,24,30 mo post-randomization)		
Subtask 1: Data collection - Complete participant study visits		
Complete required study visits, including QOL/functional status assessments	4-48	Ongoing
Obtain prescription records from local pharmacies to monitor compliance	4-48	Ongoing
Submit participant clinical data to DCC database management system	4-48	Ongoing

De-identify angiograms and submit to Angio Core Lab	4-48	Ongoing
Collect blood/urine samples for ancillary studies, if funded	4-48	Not yet funded
Submit adverse event reports to DCC and local IRB (if applicable) per required time frames	As needed	Ongoing
<i>Milestone Achieved: Data collection complete</i>	48	CONTINUING
Subtask 2: Event Reporting and Monitoring, Quality Assurance and Centralized Assessments		
DCC securely posts SAEs and Committee submits adjudications	7-30	Ongoing
DCC submits SAEs to DoD and DSMB per required time frames	7-30	Ongoing
DSMB reviews 6-mo outcomes of first 5 participants assigned to EVL/LDTAC	10	✓ Mtg held 10JAN2019
ACL performs angio readings and submits assessments to DCC	10-33	Ongoing
Site visits and data audits performed in person, 1 per site and for-cause;	12-40	First visit July 2019; Ongoing
Ongoing monitoring of site and ACL data quality and completeness by DCC		Ongoing
Write and publish trial design manuscript prior to interim look	8-14	Pending
DSMB meeting for one interim look at efficacy outcome (estimated timing)	30	Estimated date 2020
DCC coordinates DSMB meetings, prepares and securely post reports	10-43	Ongoing
<i>Milestone Achieved: Standardized assessments and QA/QC measures executed</i>	48	CONTINUING

What was accomplished under these goals?

In this Reporting Period (Year 2), trial execution has proceeded successfully on many fronts.

Study Sites: *Business agreements with all 26 (non-BCH) study sites and core laboratory have been fully executed. A Central IRB and full Reliance and/or IRB approval has been achieved for 25 of 26 sites (a 27th site, MUSC withdrew in Y01). This summary includes the addition of two study sites in Y02; one of which is active and screening/enrolling.*

Communications: *Weekly Operations Committee, Biweekly Executive Committee and monthly Steering Committee and Study Coordinator conference calls are held.*

Protocol Execution and Monitoring: *The InForm database management system, randomization system, and core laboratory and event adjudication systems are in full use. One in-person Protocol Training has been conducted in Y02 (in addition to numerous webinars) and two DSMB meetings have been held (Jan and July 2019). The first regulatory/data audit site visit occurred in July 2019 and others have been scheduled and will occur in Y03.*

Trial Tools:

a) The informed consent video produced in Y01 as an informational tool for families, described at <http://med.stanford.edu/teammate.html>, was recreated in Spanish in Y02: <https://www.youtube.com/watch?v=KnWwkHUZCv8>.

b) A video demonstrating the preparation procedure for liquid everolimus to be used by families with infants and young children randomized to everolimus was created:

<https://www.youtube.com/watch?v=CO7VtATeofU&feature=youtu.be>

Enrollment: Patient screening began in Y1 Q2; as of 9/14/19, 440 patients have been screened; 244 were potentially eligible; 159 (65%) provided consent to participate; 151 were fully eligible and 151 of a target 210 patients have been randomized (72% of total target). At the last annual report, 43 had been randomized. The enrollment rate is 55% of expected to date; and we project that enrollment will be completed in February-March 2020.

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

Drs. Sleeper, Almond and Daly attended the International Society for Heart and Lung Transplantation Annual Conference in April, 2019.

How were the results disseminated to communities of interest?

Not applicable (trial not complete).

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

1. Obtain IRB and USAMRMC HRPO approval for 1 remaining site (Children's National Med Center)
2. Continue screening and randomization of patients
3. Complete the trial design manuscript
4. Complete the Statistical Analysis Plan (SAP).
5. Continue Adjudication Committee case reviews and submission of scores.
6. Continue Angiography Core Laboratory image reviews and submission of data.
7. Conduct regulatory/data audit site visits at 50% of sites.
8. Conduct two DSMB meetings for assessment of patient safety and data quality.

4. IMPACT:

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

This randomized trial has made an impact on the field of pediatric heart transplantation by demonstrating for the first time that a collaborative clinical research network specific to pediatric heart transplantation can be successfully formed to efficiently execute multicenter research studies to improve the management and outcomes of children who have undergone heart transplantation.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

- 5. CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change

We anticipate that the original 15-month accrual (enrollment) period will be extended by approximately an additional 10 months in order to achieve the target 210 participants (completion in Feb or March 2020). The follow-up period of 30 months per participant is fixed; therefore, we will request a one year no-cost extension in the final year of the award.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Our main challenge continues to be subject accrual at a rate lower than projected despite having nearly all sites active at this time. The enrollment rate is impacted slightly lower eligibility and consent rates than estimated. Nevertheless, trial morale is high and enrollment is steady – we have completed 72% of total target (151 of 210). In Y03, one action we took was to add 2 additional sites (DiMaggio Hospital in FL and Children’s National Medical Center in Washington, DC). We have also implemented a tracking procedure for all transplants at the sites so that the DCC and CCC are able to communicate with the sites when the 5-7 month post-transplant window is opening for every potential trial patient.

Changes that had a significant impact on expenditures

Expenditures were lower than projected as the Sr. Data Manager position at the DCC and the Project Director position at the CCC (Stanford) were vacant in 2019 and filled in summer 2019. The new personnel, Ms. McGarigle and Ms. Gonzales, will commit 100% effort to the project in Y03. Our enrollment improved in Y02, but remains below target to date, causing lower overall payment to study sites for subject enrollment. Enrollment will continue in Y03. Due to lower than expected enrollment, the site monitoring visits planned for Y02 are now scheduled to occur in Y03 with associated expenditures to be made in Y03.

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

Significant changes in use or care of human subjects

The trial protocol has had seventeen amendments approved. Amendment #17 was approved by the central/single IRB at Boston Children's Hospital on 08/06/2019.

The continuing review to the Central IRB (Boston Children's Hospital) was submitted on 05/08/2019 and approved on 05/28/2019.

The continuing review by the DoD HRPO was submitted on 06/19/2019 and approved on 06/24/2019.

Significant changes in use or care of vertebrate animals

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Publications, conference papers, and presentations

Journal publications.

Published Abstract:

Bock MJ, Chau P, Kuhn MA, Martens T, Razzouk A, Chinnock RE. The Major Adverse Transplant Events (MATE) Score Applied to a Cohort of Pediatric Heart Transplant Recipients. *J Heart Lung Transpl* April 2019; 38(4), Supplement, S471-S472. DOI: <https://doi.org/10.1016/j.healun.2019.01.1199>

See Appendix for full abstract.

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

Nothing to report.

Other publications, conference papers and presentations.

Bock, M.J. (2019, October). Pediatric Heart Transplant Program Safety Update. Oral presentation at the Loma Linda University Children's Hospital Patient Safety Relations Committee Meeting, Loma Linda, CA.

ABSTRACT accepted (not yet presented):

Lee J, Castleberry C, Bock M, Auerbach SR, Rossano JW, Hollander SA, Lal AK, Pahl E, Barkoff L, Klein GL, Almond CS, Sleeper LA, Daly KP. "Accuracy of Initial Everolimus Dosing in the TEAMMATE Trial: How Well Does It Work in Pediatric Heart Transplantation?" Accepted for poster presentation at the International Society for Heart and Lung Transplantation Annual Conference in April, 2020.

Website(s) or other Internet site(s)

The following website went live in October 2018. Its purpose is to promote TEAMMATE Trial visibility and serve as an informational resource to patient families and study centers:

<http://med.stanford.edu/teammate.html>

- **Technologies or techniques**

Nothing to report.

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**

- **A Spanish language version informed consent video** was produced as an informational tool for families: : <https://www.youtube.com/watch?v=KnWwkHUZCv8>
- **An instructional video on Preparation of Liquid Everolimus** was produced for use by families participating in the trial:

<https://www.youtube.com/watch?v=CO7VtATeofU&feature=youtu.be>

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Lynn Sleeper, ScD
Project Role: PD/PI, PI of DCC
Researcher Identifier (e.g. ORCID ID): 0000-0002-8055-768X
Nearest person month worked: 0.75
Contribution to Project: No change.

Name: Kevin Daly, MD
Project Role: Co-Investigator, Co-PI of CCC
Researcher Identifier (e.g. ORCID ID): 0000-0003-4327-1532
Nearest person month worked: 0.75
Contribution to Project: No change.

Name: Christopher Almond, MD, MPH
Project Role: Co-Investigator, Co-PI of CCC
Researcher Identifier (e.g. ORCID ID): 0000-0001-7136-8337
Nearest person month worked: 0.75
Contribution to Project: No change.

Name:	Tajinder Pal Singh, MD, MSc
Project Role:	Co-Investigator/Medical Monitor
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0.3
Contribution to Project:	No change.
Name:	Shelley Miyamoto, MD
Project Role:	Co-Investigator/Director of Angiography Core Laboratory
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0.095
Contribution to Project:	No change.
Name:	Mary McGarigle
Project Role:	Senior Data Manager
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1
Contribution to Project:	Replaced Linda Massey.
Name:	Adrianna Twombly
Project Role:	Assistant Project Director
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1.3
Contribution to Project:	Ms. Twombly has provided communications and research support for the Data Coordinating Center, including development of the Trial Manual of Operations and field specifications for the Adjudication decisions and Angiogram de-identification and upload Portal.
Name:	Gloria Klein, MS, RD
Project Role:	Project Director of DCC
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1.8
Contribution to Project:	No change.
Name:	Kendra Lagerborg
Project Role:	Administrative Coordinator of DCC
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0.975
Contribution to Project:	Ms. Lagerborg provides administrative and research support for the Data Coordinating Center.
Name:	Matthew MacLean
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0.38
Contribution to Project:	Part time, as of 8/1/19

Name: Jared Wilber
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 0.5
Contribution to Project: Replacing Matthew MacLean

Name: Minmin Lu, MS
Project Role: Statistical Programmer
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 0.3
Contribution to Project: Ms. Lu has been responsible for creation and execution of statistical programs for DSMB, abstracts, and study reports and interacting with the data manager to identify data to be queried.

Name: Jane Messere, RN
Project Role: Clinical Research Associate
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 0.36
Contribution to Project: Ms. Messere reviews with the Medical Monitor the adverse event documentation that is submitted by the sites to the DCC for adjudication, requests additional materials where necessary, and responds to site queries on regulatory and reporting matters.

Name: Joanne Lee, PharmD
Project Role: Pharmacist
Researcher Identifier (e.g. ORCID ID): 0000-0002-8008-6910
Nearest person month worked: 0.3
Contribution to Project: No change.

Name: Selena Gonzales, MPH
Project Role: Project Manager of the CCC
Researcher Identifier (e.g. ORCID ID): 0000-0003-3744-111X
Nearest person month worked: 1.5
Contribution to Project: Replaced Jua Choi, PharmD, RD, CNSC

Name: Joseph Rossano, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 0.225
Contribution to Project: No change.

Name: Scott Auerbach, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-2341-0913
Nearest person month worked: 0.225
Contribution to Project: No change.

Name: Seth Hollander, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-0818-3150
Nearest person month worked: 0.225
Contribution to Project: No change.

Name: Matthew Bock, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-1357-4698
Nearest person month worked: 0.225
Contribution to Project: No change.

Name: Chesney Castleberry, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-9052-2333
Nearest person month worked: 0.0375
Contribution to Project: No committed effort beyond 7/1/19

Name: Elfriede Pahl, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 0.225
Contribution to Project: No change.

Name: Ashwin Lal, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-0935-6858
Nearest person month worked: 0.225
Contribution to Project: No change.

Name: Aecha Marion Ybarra, MD
Project Role: Co-Investigator/Site PI
Researcher Identifier (e.g. ORCID ID): n/a
Nearest person month worked: 0.19
Contribution to Project: Replaced Dr. Castleberry as Co-Investigator/Site PI at Washington University

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

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

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

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

9. APPENDICES:

Published Abstract

Bock MJ, Chau P, Kuhn MA, Martens T, Razzouk A, Chinnock RE. The Major Adverse Transplant Events (MATE) Score Applied to a Cohort of Pediatric Heart Transplant Recipients. *J Heart Lung Transpl* April 2019; 38(4), Supplement, S471-S472.

DOI: <https://doi.org/10.1016/j.healun.2019.01.1199>

THE MAJOR ADVERSE TRANSPLANT EVENTS (MATE) SCORE APPLIED TO A COHORT OF PEDIATRIC HEART TRANSPLANT RECIPIENTS

Bock MJ, Chau P, Kuhn MA, Martens T, Razzouk A, Chinnock RE.

Purpose

The MATE score evaluates a surrogate end-point comprised of MATEs that predict graft loss. The first major pediatric heart transplant (PHTX) drug study, TEAMMATE, will use the MATE score as a primary end point. We have applied a calcineurin inhibitor (CNI) minimization strategy via early transition to a proliferation signal inhibitor (PSI) since 03/11, similar to the protocol employed in the TEAMMATE study. We sought to apply the MATE score to our population.

Methods

All PHTX patients between 03/11-12/14 surviving to 4-mo post-HTX with 36-mo of follow-up formed the study cohort. An equal number of HTX patients from a similar prior period formed the control cohort. Study subjects followed the early transition to PSI protocol, while the control subjects remained on mycophenolate (MMF). Statistical analyses were similar to those described for the TEAMMATE study.

Results

Twenty-seven subjects formed each group. At study end, 77% of study subjects vs. 24% of control subjects remained on protocol. A baseline-adjusted comparison of mean MATE-3 scores at 36-mo post-HTX did not suggest a difference in efficacy between the groups (ANCOVA $p = 0.50$). The longitudinal linear mixed effects regression (lmer) model assessing differences in MATE-3 scores over time was not different between the groups either ($p = 0.74$). Safety, assessed by Tukey's Honest Significant Difference between 36-mo MATE-6 scores, was similar between the groups as well. An upper 95% confidence limit difference of +0.56 was found and is within the acceptable safety range. Lower age (<1 yr) was found to predict lower MATE-3 scores (ANCOVA $p = 0.02$; lmer $p = 0.04$). In non-infants, there was a trend toward lower MATE-3 scores in the PSI group (Figure 1).

Conclusion

In this small group of PHTX patients following treatment regimens similar to those found in the TEAMMATE study with a high control cross over rate, safety and efficacy seem to be similar. In older patients however, early transition to a PSI-based regimen may improve long-term outcomes.

Previously published:

Sleeper LA, Daly KP, Rossano JW, Desai M, Auerbach S, Bock MJ, Castleberry CD, Fenton M, Hollander SA, Lal A, Pahl E, Almond CS. Design of the TEAMMATE Trial for children with heart transplant and development of a novel efficient endpoint. Society for Clinical Trials 39th Annual Meeting, Portland, OR; May 2018.