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TITLE: Multicenter Randomized Trial of Everolimus in Pediatric Heart Transplantation

PRINCIPAL INVESTIGATOR: Sleeper, Lynn A.

CONTRACTING ORGANIZATION: Children's Hospital Corporation
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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 25 centers, with leadership at Boston Children's Hospital (Data Coordinating Center) and Stanford University (Clinical Coordinating Center). At the time of this annual report, 21 of 25 centers are fully initiated and able to screen and enroll patients. A total of 43 patients have been randomized. Additional accomplishments in Year 01 include two in-person Protocol Certification Trainings; implementation of a single/central Institutional Review Board; successful execution of two Data and Safety Monitoring Board meetings and a Steering Committee meeting; development of MATE Adjudication Guidelines; and creation of an informed consent video for families, the Data Management system and the portal for upload of coronary angiograms to the Angiographic Core Laboratory.

15. SUBJECT TERMS

Heart transplantation; children; immunosuppression; randomized clinical trial

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	22	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

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 mofitil (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 25 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	22 fully approved 3 new in process
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 #6 approved 7/9/18
Submit annual single IRB report for continuing review	Annually	✓

Milestone Achieved: Approval by Military HRPO and FDA	1	✓
Milestone Achieved: Local IRB approval at Study Sites and Angio Core Laboratory	3	**COMPLETE** for original sites
Subtask 2: Execute financial agreements / subawards		
Coordinate with CCC, 24 Sites (22 original, 3 new) and Core Lab to execute Subcontracts/ CTAs	1-3	23 fully executed 2 new in process
Execute Consultant Agreements with Adjudication Committee members	1-3	✓
Milestone Achieved: All Subcontracts and Consultant Agreements executed	1-3	**COMPLETE** for original sites
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
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	✓ 51 Study & Transplant Coords + 26 PIs

		trained
Milestone Achieved: Research staff trained	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	51 CRFs finalized
Create Trial and Angio Core Lab Manuals of Operation (MOO)	2-3	In process (80% and 95% complete)
Develop Administrative website to post trial materials and secure documents	1-3	✓
Develop and test database management and randomization systems	2-3	48 of 51 CRFs in use (94%)
Angio Core Lab to obtain license from Ambra Health for secure image transfer	1	✓ 12/14/17
Milestone Achieved: Study systems developed and functional for trial launch	3	Nearly 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	58 screened 43 of target 210 randomized
Teleconference with SCs every other week and site PIs monthly	4-18	✓
Milestone Achieved: Recruitment and randomization of 210 participants	18	**CONTINUING**

What was accomplished under these goals?

In this Reporting Period (Year 1), trial execution has proceeded successfully on many fronts.

Study Sites: Business agreements with all 22 original study sites and core laboratory have been fully executed. A Central IRB and full Reliance and/or IRB approval has been achieved for all original sites. We added 3 additional study sites in Q3 and their start-up activities are partially complete. An application was submitted to Health Canada to conduct the trial at a Canadian site and approval was granted; availability of study drug in Canada is under investigation.

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 and randomization systems were created and are live. Two in-person Protocol Trainings have been conducted and two DSMB meetings have been held.

Trial Tools: A public website was created to increase trial visibility and as a resource to families: http://med.stanford.edu/teammate.html. An informed consent video was also produced as an informational tool for families: https://www.youtube.com/watch?v=UL9yXW7QjQo&list=UUOvJLyjwak1N6Jn9RA2XrSw.

Enrollment: Patient screening began in Q2; as of 9/14/18, 99 patients have been screened; 65 were potentially eligible; 48 (74%) provided consent to participate; 46 were fully eligible and 43 of a target 210 patients have been randomized (20% of target). The randomization rate is below projected (enrollment is 42% of expected to date) due to the staggered start-up time of the study sites. We expect the enrollment rate to increase in Y02 with a full complement of sites and the completed informational resources to facilitate informed consent.

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, 2018.

How were the results disseminated to communities of interest?

Nothing to report.

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

1. Obtain fully executed business agreements with all remaining parties (2 of the 3 new sites).
2. Obtain IRB approval for the 3 new sites
3. Obtain USAMRMC HRPO approval for the 3 new sites
4. Continue screening and randomization of patients
5. Finalize the Trial Manual of Operations
6. Complete the Statistical Analysis Plan (SAP).
7. Begin Adjudication Committee case reviews and submission of scores.
8. Begin Angiography Core Laboratory image reviews and submission of data.
9. Conduct an in-person DSMB meeting for assessment of patient safety (pre-specified to be held when the first 10 everolimus patients have completed 6 months of follow-up) - 10 JAN 2019.

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 8 months in order to achieve the target 210 participants. The follow-up period of 30 months per participant is fixed; therefore, we are likely to request a no-cost one year 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 is subject accrual at a rate lower than projected due to staggered startup times of the study sites and a slightly lower eligibility rate of existing patients than estimated. In response to these challenges, we have selected and added 3 additional sites which will be fully on board before the end of 2018 and the potential for one Canadian site (Stollery Children's Hospital) in 2019. We have also implemented increased communication between Trial chairs and Site investigators to review eligibility of each transplant patient and implemented protocol amendments clarifying some of the trial eligibility criteria.

Changes that had a significant impact on expenditures

Expenditures for Year 1 are less than projected due to delays in hiring some staff and fewer randomizations in Year 1 than estimated, leading to fewer payments to study sites for enrollment.

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 six amendments approved. Amendment #6 was approved by the central/single IRB at Boston Children's Hospital on 7/9/18.

The Continuing Review to Dept. of Defense HRPO was submitted on 7/10/18 and approved on 7/16/18.

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.

ARTICLE - TRIAL ENDPOINT DEVELOPMENT (pre-award work):
Almond CS, Hoen H, Rossano JW, Castleberry C, Auerbach SR, Yang L, Lal AK[6], Everitt MD, Fenton M, Hollander SA, Pahl E, Pruitt E, Rosenthal DN**,** McElhinney DB, Daly KP, Desai M; Pediatric Heart Transplant Study (PHTS) Group Registry. Development and validation of a major adverse transplant event (MATE) score to predict late graft loss in pediatric heart transplantation. *J Heart Lung Transplant.* 018 Apr;37(4):441-450. doi: 10.1016/j.healun.2017.03.013. Epub 2017 Mar 24.

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

ABSTRACT:

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.

Other publications, conference papers and presentations.

Castleberry C., St. Louis Children's Hospital, Grand Rounds 2018, "Research in Pediatric Heart Transplantation"

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

The following website was under development at the end of Year 1 (and is now live as of Oct 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**

• **An informed consent video** was produced as an informational tool for families: https://www.youtube.com/watch?v=UL9yXW7QjQo&list=UUOvJLyjwak1N6Jn9RA2XrSw • **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:	Linda Massey
Project Role:	Senior Data Manager
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0
Contribution to Project:	Left project in May
Name:	Julia Burns
Project Role:	Assistant Project Director
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0
Contribution to Project:	Left project in July.
Name:	Adrianna Twombly
Project Role:	Assistant Project Director
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1.5
Contribution to Project:	Replaced Julia Burns. 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:	Pascale Chataigne
Project Role:	Administrative Coordinator of DCC
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	0
Contribution to Project:	Left project in May.

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:	Replaced Pascale Chataigne. Ms. Lagerborg has provided 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:	0.75
Contribution to Project:	No change.
Name:	Minmin Lu
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 and study reports and interacting with the data manager to identify data to be queried.
Name:	Jane Messere
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:	Jua Choi, PharmD, RD, CNSC
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:	Left in September.

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:	0.225
Contribution to Project:	No change.

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.

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.

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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

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.

DESIGN OF THE TEAMMATE TRIAL FOR CHILDREN WITH HEART TRANSPLANT AND DEVELOPMENT OF A NOVEL EFFICIENT ENDPOINT

Sleeper LA, Daly KP, Rossano JW, Desai M, Auerbach S, Bock MJ, Castleberry CD, Fenton M, Hollander SA, Lal A, Pahl E, Almond CS

BACKGROUND: Clinical research in pediatric heart transplant has historically been conducted to assess short-term outcomes at single centers. Efficient approaches are needed to test hypotheses related to long-term outcome.

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. Late mortality is driven by 6 major adverse transplant events (MATE): acute cellular rejection (ACR), antibody-mediated rejection, coronary artery vasculopathy (CAV), post-transplant lymphoproliferative disorder, infection, and chronic kidney disease (CKD). In recent years, everolimus (EVL), a proliferation signal inhibitor, in combination with low-dose tacrolimus (LDTAC), has emerged as a potential treatment that may improve longer-term survival by reducing the risk of CAV, CKD and ACR, as well as cytomegalovirus infection.

THE CHALLENGE: Evaluation of an immunosuppressive regimen to reduce the rate of long-term complications of transplant is hindered by a large sample size requirement and lengthy follow-up in order to achieve sufficient power to detect treatment differences. The MATE Score was developed by a network of pediatric heart transplant investigators; it was validated against long-term registry outcomes and then approved by the FDA, paving the way for implementation of an efficient trial design.

DESIGN: The FDA-regulated, multicenter randomized TEAMMATE Trial network infrastructure was built in 2017 and launched enrollment in 2018. The trial is led by a Clinical Coordinating Center at Stanford University and a Data Coordinating Center at Boston Children's Hospital. Innovations include the MATE score and the use of a central IRB for over 20 sites to facilitate efficient trial start-up. The target of 210 patients will be randomized to either the standard TAC/MMF or EVL/LDTAC at 6 months post-transplant. The primary efficacy and safety endpoints are two forms of the MATE score. Follow-up is 2.5 years per subject. Central adjudication of

clinical MATE events and a core laboratory for angiogram interpretation are in place to minimize variance.

CONCLUSIONS: Leveraging the cumulative burden of multiple complications into a single, continuous validated endpoint enables the TEAMMATE trial to test a hypothesis regarding long-term outcome with relatively short follow-up. This talk will highlight trial endpoint development, statistical power considerations, and the logistics of efficiently launching a complex multicenter trial with multiple stakeholders. We anticipate that the TEAMMATE trial will result in FDA approval of the first immunosuppression regimen for pediatric heart transplantation and that the trial infrastructure will facilitate the development of a sustainable clinical research network for the pediatric heart transplant field.