Trial Innovation Network (TIN)
Trial Innovation Unit (TIU)

How the ICTR can help investigators plan and execute clinical trials

ICTR Town Hall March 2021
Objective

• Introduce the JH ICTR Trial Innovation Unit (TIU) and the NCATS Trial Innovation Network (TIN)

• Describe the relationship between the TIU and the TIN

• Educate how the TIU can assist local investigative teams planning and executing clinical trials
Acronyms

**Trial Innovation Network (TIN)**
- A Clinical & Translational Science Awards (CTSA) program
- Focuses on operational innovation
- Goal: Execute trials better, faster, and more cost-efficiently

**60+ CTSA awardee institutions**

**Trial Innovation Centers (TICs)**
- Duke University-Vanderbilt University
- University of Utah
- Johns Hopkins-Tufts

**Recruitment Innovation Center (RIC)**
- Vanderbilt University

**Trial Innovation Unit (TIU) at the JHU ICTR**
Trial Innovation Network: Therapeutic Diversity of TIN Supported Studies

% of Therapeutic Areas Represented

- Cardiovascular Diseases (14%)
- Infectious Diseases (8%)
- Neurology (8%)
- Pediatric Disciplines (8%)
- Pulmonary Diseases (5%)
- Oncology (4%)
- Diabetes (3%)
- Gastroenterology (3%)
- Hematology (3%)
- Trauma (3%)
- Other (41.0%, click for details)
Addressing Barriers to Clinical Research across the Trial Innovation Network

BARRIERS

- Flawed design
- Inefficient conduct
- Lack of stakeholder engagement
  - Eligibility criteria too burdensome
- Delays in start up, e.g. IRB review, contract execution
- Fragmented operating models
  - Infrastructure rebuilt
- Recruitment challenges
  - Long timelines, altered study designs
- High costs of data collection & management
  - Inadequate data collection & management

TIN OPPORTUNITIES

- Consultations with clinical trial, disease, statistical, and recruitment experts
- Specialized support from the Recruitment Innovation Center
- Single IRB support and oversight, Standard Agreement toolkits
- Streamlined support to implement trials, Clinical Coordinating Center assistance
- Recruitment Innovation Center support with recruitment and retention planning
- Streamlined support to implement trials, Data Coordinating Center assistance
Trials Innovation Network (TIN) vs JH ICTR Trial Innovation Unit (TIU)

Studies within JH ICTR

The JH ICTR Trial Innovation Unit (TIU) offers local investigators the opportunity to centralize services, improve the strength and efficiency of research proposals, and foster local, collaborative development of proposed research.

The TIU is charged with providing support for small, local and multisite translational studies needing strategic support for tests of study generalizability from smaller to larger cohorts to be implemented primarily at JH or within the JH Clinical Trial Research Network.

Studies across CTSA Network

The Trial Innovation Network (TIN) offers investigators the opportunity to request consultations and resources for large, multicenter clinical trials and studies.

These are designed to help investigators, for example, develop proposals into protocols, enhance study operations, or improve recruitment and retention. Some consultations developed into clinical protocols may be implemented across the Network CTSA Program.
Trial Innovation Unit (TIU)
Addressing Barriers to Clinical Research within the Trial Innovation Unit

**BARRIERS**
- Flawed design
  - Inefficient conduct
- Inadequate data collection & management
- Flawed design
  - Eligibility criteria too burdensome
- Delays in start up, e.g. IRB review, contract execution
- Fragmented operating models
  - Infrastructure rebuilt
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Consultations with local clinical trial, disease, statistical, and recruitment experts
Specialized support from the Recruitment Innovation Unit
JHM Single IRB coordination, Standard Agreement toolkits
Referral to ICTR resources/cores for Clinical Coordinating Center, Data Coordinating Center, and Recruitment/Retention Planning depending on investigator needs (see ICTR website)
TIU Consultation Potential Components

• Cohort discovery via PCORNet and TriNetX mechanisms
• Site selection and readiness assessment within and beyond the Johns Hopkins Clinical Research Network
• Cost assessment: protocol and budget development
• Agreement and subcontract negotiation coordination
• Single IRB coordination and review in collaboration with the Regulatory Knowledge and Support Core service
• Method development to track study performance and outcomes at the local Hub and affiliated sites
• Organization and trial execution strategy consultation
• Direction and strategy for grant preparation
Leveraging Existing CTSA Resources and Personnel to:

• Improve research study design, trial operations and analysis plans
• Explore opportunities for single- and multicenter trial innovation
• Assess translational pathway and readiness or for multicenter trials
• Provide strategic assistance with grant applications and letters of support
• Improve diversity and community engagement in clinical trials
• Improve the overall stewardship, efficiency, accountability, and transparency of clinical trials
TIU Triage for JHU Investigators

**Step 1:**
Investigator may request a TIU consultation during the grant planning (pre-funding) or grant implementation (funded) stages by completing the TIU Proposal Intake Form via the ICTR website

https://ictr.johnshopkins.edu/collaboration/collaborations/trial-innovation-unit-tiu

**Step 2:**
A TIU representative contacts the Investigator within 5 business days to schedule brief phone call to review the TIU Proposal Intake Form and to schedule Initial Consult
TIU Triage for JHU Investigators

Step 3:
TIU Initial Consultation is scheduled as a one to two hour meeting with various content experts. Follow-up meetings may also occur. TIU consultation to complete within 30-60 days.

Step 4:
TIU Proposal Assessment Team meets monthly to discuss recommendations, which may include:

- TIU Comprehensive Consult
- Referral to ICTR Studio
- Referral to specific ICTR Core(s)
- Referral to TIN for consultation
- No further support
# Institutional Clinical Trial Expertise

(*University of Maryland*)

<table>
<thead>
<tr>
<th>Center Leadership</th>
<th>Centers of Excellence</th>
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<tbody>
<tr>
<td>Karen Bandeen-Roche, PhD, MS</td>
<td>ICTR Deputy Director for Biostatistics and Research Design; Chair, Department of Biostatistics</td>
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<tr>
<td>Michael Terrin, MD, MPH*</td>
<td>Biostatistics Core; Claude D. Pepper Older Americans Independence Center (UMD)</td>
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<tr>
<td>Jay S. Magaziner, PhD, MSHyg*</td>
<td>Center for Research on Aging; Chair, Department of Epidemiology &amp; Public Health (UMD)</td>
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<tr>
<td>Douglas Jabs, MD, MBA, MS</td>
<td>Johns Hopkins Center for Clinical Trials and Evidence Synthesis</td>
</tr>
<tr>
<td>Gayane Yenokyan, MD, PhD</td>
<td>Johns Hopkins Biostatistics Center</td>
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<tr>
<td>Jacky Jennings, PhD, MPH</td>
<td>Biostatistics, Epidemiology and Data Management (BEAD) Core; Center for Global Health; Urban Health Institute</td>
</tr>
<tr>
<td>Gary Rosner, SCD</td>
<td>Quantitative Sciences Program and Biostatistics/Bioinformatics, Oncology</td>
</tr>
<tr>
<td>Alvaro Munoz, PhD</td>
<td>Epidemiology and Methodology, Biostatistics</td>
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<tr>
<td>Daniel Hanley, MD</td>
<td>Brain Injury Outcomes Division, Clinical Trial Coordinating Center</td>
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<tr>
<td>Susumu Mori, PhD</td>
<td>Center for Brain Imaging Science</td>
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<tr>
<td>James Tonascia, PhD</td>
<td>Curtis L. Melnert Professorship in Clinical Trials</td>
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<tr>
<td>Jose Coresh, MD, PhD</td>
<td>George W. Comstock Center for Public Health Research and Prevention</td>
</tr>
<tr>
<td>Lawrence Appel, MD, MPH</td>
<td>Welch Center for Prevention, Epidemiology, and Clinical Research</td>
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<tr>
<td>G. Caleb Alexander, MD, MS</td>
<td>Center of Excellence in Regulatory Science and Innovation; Center for Drug Safety &amp; Effectiveness</td>
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<tr>
<td>Janet Holbrook, PhD</td>
<td>Center for Drug Safety &amp; Effectiveness; Johns Hopkins Center for Clinical Trials and Evidence Synthesis</td>
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<tr>
<td>Frank C. Curriero, PhD</td>
<td>Spatial Science for Public Health Center</td>
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<tr>
<td>Barry Greenberg, PhD</td>
<td>Institute for the Prevention and Treatment of Alzheimer’s Disease at Johns Hopkins</td>
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<tr>
<td>Ellen MacKenzie, PhD</td>
<td>Major Extremity Trauma Research Consortium (METRC)</td>
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<tr>
<td>Homayoon Farzadegan, PhD and Joseph Margolick, MD, PhD</td>
<td>Johns Hopkins Biological Repository</td>
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<tr>
<td>Bonni Wittstadt, MLIS</td>
<td>Data Services Consulting, Sheridan Libraries</td>
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<tr>
<td>Stephen N. Davis, MBBS</td>
<td>Institute for Clinical and Translational Research, UMD</td>
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<tr>
<td>Daniel Ford, MD, MPH</td>
<td>Institute for Clinical and Translational Research, JHU</td>
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<tr>
<td>Diana Gumas, MS</td>
<td>Core for Clinical Research Data Acquisition; Precision Medicine Analytics Platform</td>
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<tr>
<td>Neal Fedarko, PhD</td>
<td>Clinical Research Unit Core Laboratory</td>
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<tr>
<td>Bonnie Woods, MS/ITS, MLA</td>
<td>Center for Clinical Natural Language Processing</td>
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<tr>
<td>Jonathan Weiner, DrPH</td>
<td>Center for Population Health Information Technology</td>
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<tr>
<td>Katherine Clegg Smith, PhD</td>
<td>Center for Qualitative Studies in Health and Medicine</td>
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<tr>
<td>Sanjay K. Jain, MD</td>
<td>Center for Infection and Inflammation Imaging Research</td>
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<tr>
<td>Paul G. Auwaerter, MD, MBA</td>
<td>Johns Hopkins POC-IT Center</td>
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<tr>
<td>Yukari Manabe, MD</td>
<td>Center for Point-of-Care Tests for Sexually Transmitted Diseases</td>
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<tr>
<td>Robert Bollinger, MD, MPH</td>
<td>Center for Clinical Global Health Education</td>
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<tr>
<td>Cynthia Sears, MD</td>
<td>Microbiome Center for Immunotherapy</td>
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<tr>
<td>Alex Szalay, PhD</td>
<td>Institute for Data Intensive Engineering and Science</td>
</tr>
<tr>
<td>Jamie Combazara, PhD</td>
<td>Maryland Advanced Research Computing Center (MARCC)</td>
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<tr>
<td>Dwight Raum, BS and Paul Nagy, PhD</td>
<td>Johns Hopkins Medicine Technology Innovation Center</td>
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<tr>
<td>Ralph Semmel, PhD</td>
<td>Johns Hopkins University Applied Physics Laboratory</td>
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<tr>
<td>David Horrocks, MBA, MPH</td>
<td>Chesapeake Regional Information System for Our Patients (CRISP) Database</td>
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TIU Comprehensive Consultation Assessment

Projects that are or have the potential to be:
• Single- or small, local, multi-site project
• Innovative, translational research
• Feasibly budgeted for implementation

Projects that have or may have:
• Adequate number of trained personnel throughout the study lifecycle
• Attainable recruitment and retention goals
• Opportunity for collaboration across CTSA sites and NIH ICs
TIN and TIU Overview

TIU Consult Feature: The AERO Trial
TIU Consult Highlight: The AERO Trial

PI: Alexander Hillel, MD

Study Design: Interventional

Primary Outcome: To assess the dilation interval (time between surgery) in patients with Laryngotracheal Stenosis

# Estimated Sites and Subjects: 2 sites; 128 subjects

Study Duration: 60 months

Participant Duration: 18 months
TIU Consult Highlight: The AERO Trial

TIU Intake: 5/8/2020
Initial Meeting: 5/22/2020
TIU Initial Consultation: 7/9/2020
ICTR Studio: 7/30/2020
TIU Comprehensive Consultation Start: 8/6/2020
TIU Comprehensive Consultation Wrap-up: 9/23/2020
Grant Submission: 10/21/2020
TIU Consult Highlight: Investigator Perspective

Ioan Lina, MD
Co-Investigator
The AERO Trial
Mechanistic Study of Everolimus in Laryngotracheal Stenosis

*Adjuvant EveRolimus Outcomes (AERO)*

PI: Zandy Hillel, MD, Department of Otolaryngology

Co-I’s:
- Alexander Gelbard, MD Vanderbilt Otolaryngology
- Dan Brennan, MD Johns Hopkins Transplant Medicine
- Ioan Lina, MD Johns Hopkins Otolaryngology

*JOHNS HOPKINS MEDICINE*
Phase II Placebo-controlled Trial

1) **Study arms:**
   1. Experimental – Everolimus
   2. Control – Placebo control

2) **Study population:** Adult laryngotracheal stenosis patients with a surgical [dilation] interval < 18 months

3) **Sample size:** 128 patients, 64 patients in each arm.

4) **Intervention:** Everolimus 1mg bid titrated to level of 1-4 ng/mL

5) **Randomization:** Covariate adaptive randomization to balance age, comorbidities, and disease severity.
Laryngotracheal Stenosis (LTS)
LTS is a life-threatening fibrotic disease that narrows the airway.

Physiologic Limitations

Normal

iSGS

PFTs

Pressure distributions (cm H2O)

Exp.

Inso.

iSGS
## Surgery Remains the Only Treatment Option

<table>
<thead>
<tr>
<th></th>
<th>Dilation</th>
<th>Laryngotracheoplasty</th>
<th>Cricotracheal Resection</th>
<th>Tracheal Resection</th>
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<tbody>
<tr>
<td>Total Procedures</td>
<td>298</td>
<td>42</td>
<td>28</td>
<td>16</td>
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<tr>
<td>Primary Procedure</td>
<td>91</td>
<td>15</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Subsequent Procedure (%)</td>
<td>64 (70%)</td>
<td>5 (33%)</td>
<td>1 (10%)</td>
<td>4 (36%)</td>
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<tr>
<td>Complication</td>
<td>2 (1%)</td>
<td>14 (33%)</td>
<td>9 (32%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>2 (13%)</td>
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</tbody>
</table>

Endoscopic Dilation is a Common Surgery Usually with a Consistent Time Interval
mTOR Inhibition Improves Survival in LTS Mice

mTOR Inhibition Decreases Tracheal Lamina Propria Fibrosis at 21 days

Human LTS is a CD4 mediated disease

mTOR Inhibition Reduces CD4+ T-cells and Macrophages

Hypothesis & Outcome Measures

• **Hypothesis**: mTOR inhibition with Everolimus will reduce fibrosis in LTS patients

• **Primary Objective**:  
  – Dilation interval (time between surgery)

• **Secondary Objectives**:  
  – Voice and breathing outcomes  
  – Voice, breathing, global QOL patient reported outcomes  
  – Histopathology of fibrosis  
  – Immune cell and fibroblast molecular changes  
  – Drug toxicity and adverse events
Multicenter Study:
Hopkins & Vanderbilt

- Large LTS Patient Populations
- More Severe Disease
- 2 leading centers in PCORI-sponsored longitudinal trial
- Work closely with Patient Advocacy Group: Living with Idiopathic Subglottic Stenosis
Questions for the Studio

• How do we develop a Safety Plan
• Patient Recruitment and Retention
• Study Design Components
  – 2:1 ratio Everolimus to placebo
  – Extend course to 3 months
  – Cross over
• Follow-Up Study – Going a step beyond
## Hopkins Patient Data

<table>
<thead>
<tr>
<th>YEAR</th>
<th>TOTAL NUMBER OF PROCEDURES</th>
<th>NEW PATIENTS</th>
<th>TOTAL PATIENTS</th>
<th>UNIQUE PATIENTS W/ SEVERE DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-15</td>
<td>88</td>
<td>43</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>2015-16</td>
<td>81</td>
<td>39</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td>2016-17</td>
<td>91</td>
<td>43</td>
<td>64</td>
<td>29</td>
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<td>2017-18</td>
<td>126</td>
<td>64</td>
<td>101</td>
<td>40</td>
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<td>2018-19</td>
<td>131</td>
<td>51</td>
<td>94</td>
<td>40</td>
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<tr>
<td>2019-20</td>
<td>113</td>
<td>45</td>
<td>91</td>
<td>36</td>
</tr>
<tr>
<td>TOTALS</td>
<td>630</td>
<td>285</td>
<td>462</td>
<td>184</td>
</tr>
</tbody>
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TriNetX: Patients treated for LTS

30 HCOs (nationally)
- 4850 unique patients
- Rate of Arrival (50.7 monthly)

At Johns Hopkins Hospital
- 210 unique patients
- Rate of Arrival (5.5 monthly)
Patient-Centered Clinical Trial Design
Survey Results from Patient Group
Q1: Willing to enroll in clinical trial?

Answered: 323    Skipped: 0

91%
Survey Results from Patient Group
Q2: Willing to travel 200 miles for 6 visits?

Answered: 323    Skipped: 0

82%
Study Design

Experimental Group
Everolimus

Initiation of Everolimus

Randomization

Control Group
Placebo

Initiation of Placebo

Postoperative Follow up

Clinical Exam & History
Laryngoscopy
Labs
Voice Assessment

Day 0
Day 7
Day 14
Day 28
Day 42

Post-Treatment Operative Assessment

Assessment of Treatment
Bronchoscopy
Biopsy

42 Days

Stop Placebo

42 Days

Stop Everolimus
Data and Safety Monitoring Plan

• Data Integrity and QA Monitoring
  – DCC
• Data and Safety Monitoring Board (DSMB)
• FDA Good Clinical practice standard for data and quality management
Institutional and National Resources

- Investigational Drug Service
- sIRB office
- Recruitment and Retention Innovation Center (RIC) at Vanderbilt
- Statistical review
You may be thinking...

• **Does a TIU consultation require funding?**
  TIU consultation is a no cost (grant supported) opportunity to introduce and leverage ICTR resources, some of which may be fee for service.

• **Is the TIU an academic CRO?**
  The TIU is a consultation service managed by the ICTR and the division of Brain Injury Outcomes (BIOS). BIOS operates as an academic research organization and can manage multicenter protocols for a fee.

• **Can the TIU provide references from investigators assisted in the past?**
  The TIU web page on the ICTR website is currently being updated to include this information. Check back often for updates.

• **What are other available ICTR resources?**
  There are many ways the ICTR can help! See the website for more information: [https://ictr.johnshopkins.edu/](https://ictr.johnshopkins.edu/) or email ictr@jhmi.edu
TIU and TIN Overview

Questions?
Thank you!