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

How the ICTR can help investigators plan and execute clinical trials

ICTR Town Hall March 2021

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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

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Trial Innovation Network (TIN)

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

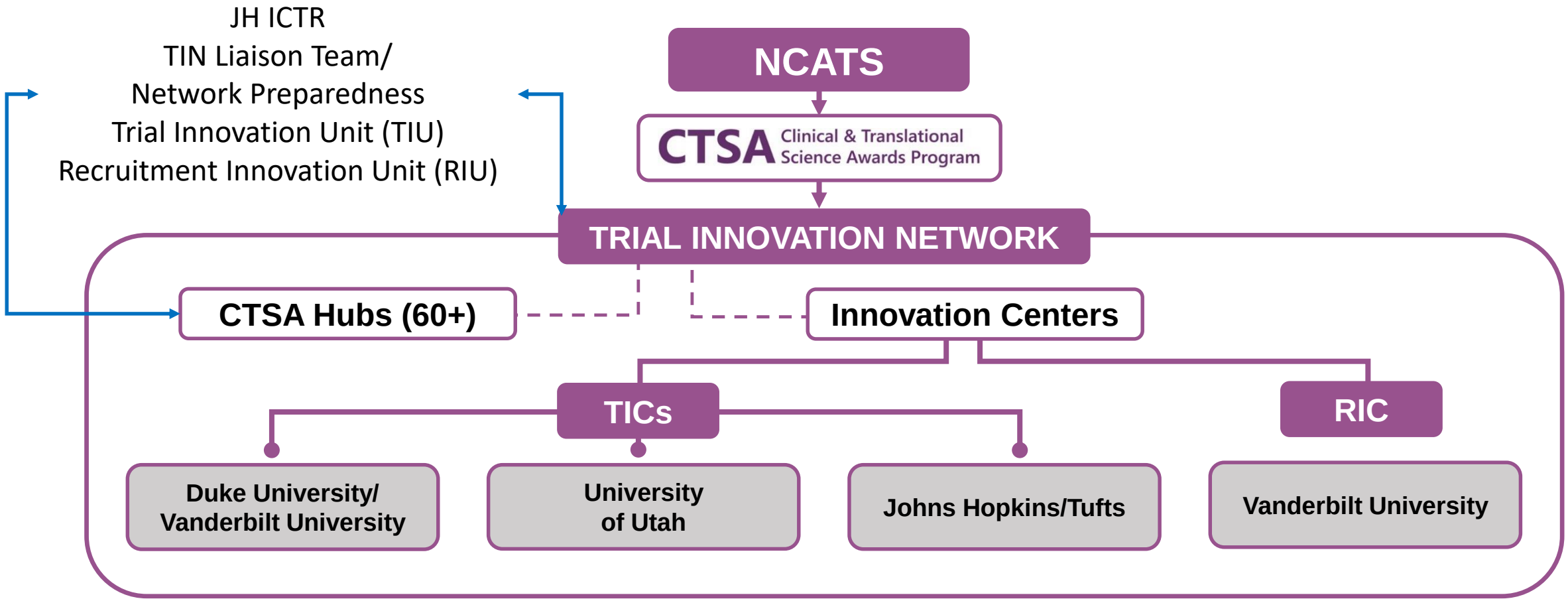
Recruitment Innovation Center (RIC)

- Vanderbilt University

Trial Innovation Unit (TIU) at the JHU ICTR

Johns Hopkins
Institute for Clinical & Translational Research

Trial Innovation Network Structure



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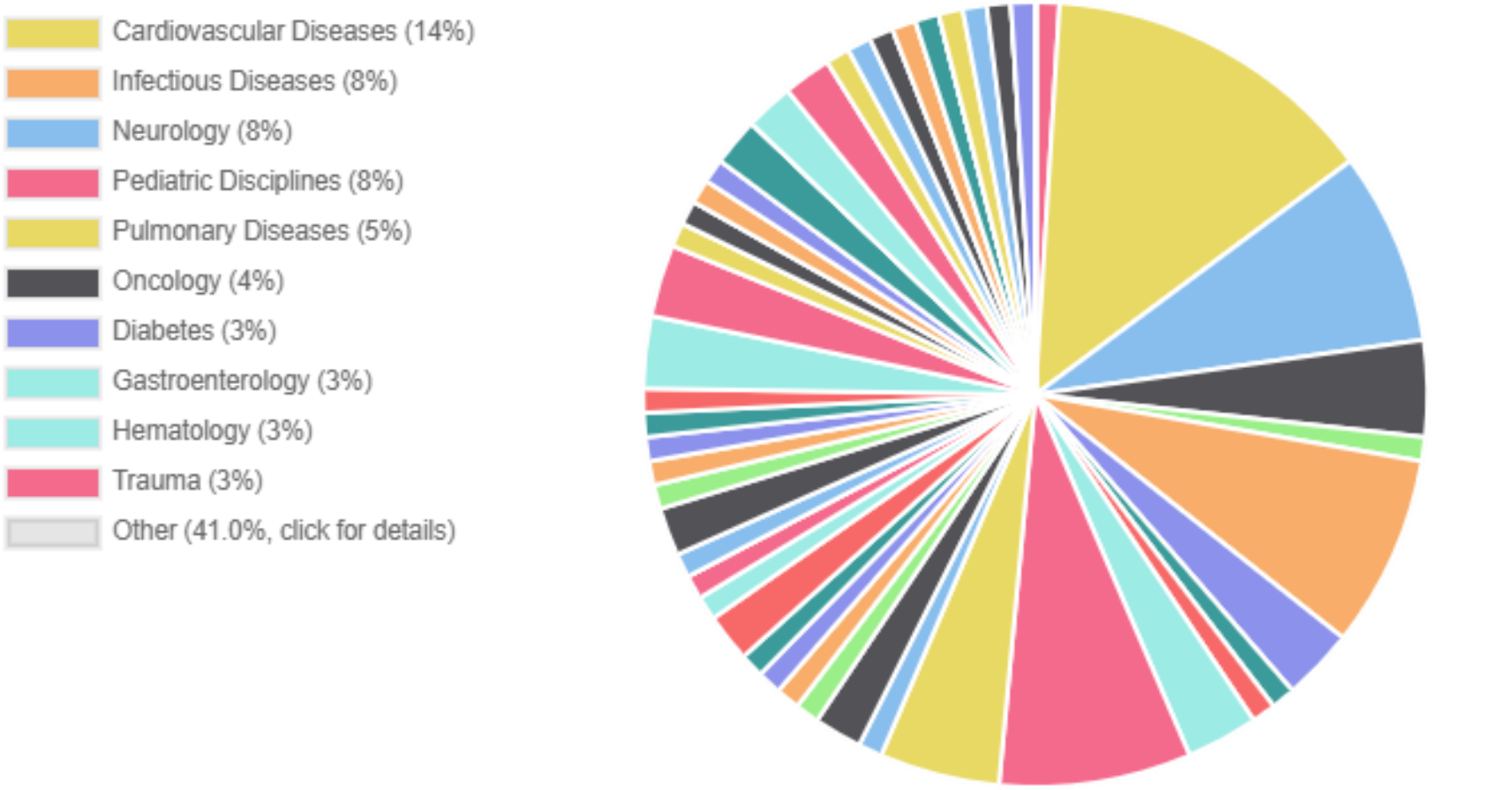
Trial Innovation Network: Therapeutic Diversity of TIN Supported Studies

% of Therapeutic Areas Represented



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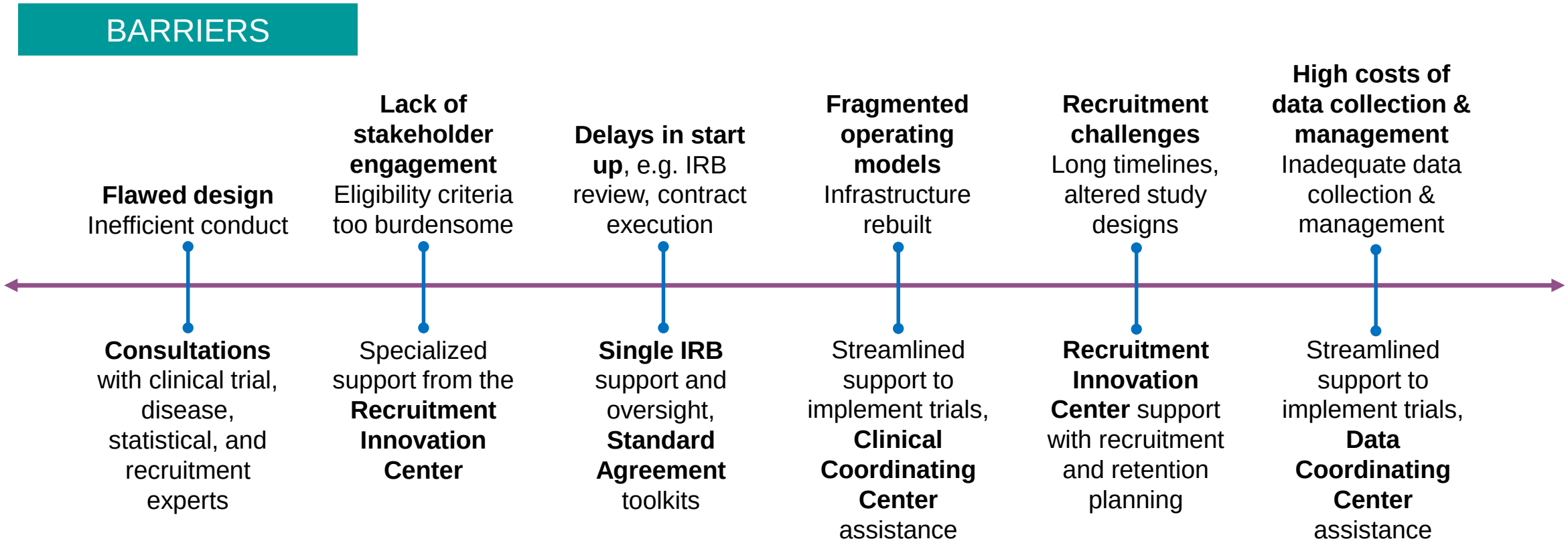
Addressing Barriers to Clinical Research across the Trial Innovation Network



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Trial 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**.

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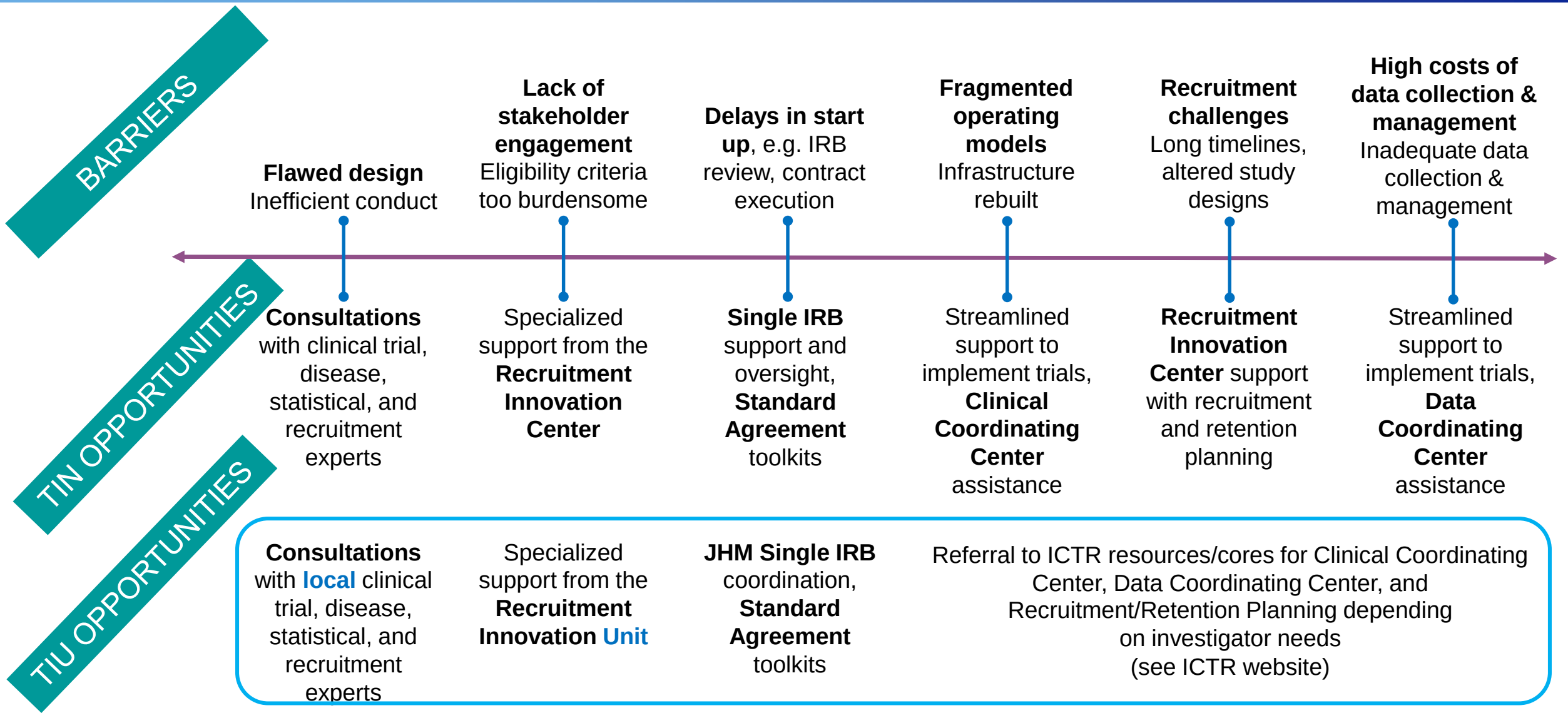
Trial Innovation Unit (TIU)

Addressing Barriers to Clinical Research within the Trial Innovation Unit



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

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Institutional Clinical Trial Expertise (*University of Maryland)

Center Leadership	Centers of Excellence
Karen Bandeen-Roche, PhD, MS	ICTR Deputy Director for Biostatistics and Research Design; Chair, Department of Biostatistics
Michael Terrin, MD, MPH*	Biostatistics Core; Claude D. Pepper Older Americans Independence Center (UMD)
Jay S. Magaziner, PhD, MSHyg*	Center for Research on Aging; Chair, Department of Epidemiology & Public Health (UMD)
Douglas Jabs, MD, MBA, MS	Johns Hopkins Center for Clinical Trials and Evidence Synthesis
Gayane Yenokyan, MD, PhD	Johns Hopkins Biostatistics Center
Jacky Jennings, PhD, MPH	Biostatistics, Epidemiology and Data Management (BEAD) Core; Center for Global Health; Urban Health Institute
Gary Rosner, SCD	Quantitative Sciences Program and Biostatistics/Bioinformatics, Oncology
Alvaro Munoz, PhD	Epidemiology and Methodology, Biostatistics
Daniel Hanley, MD	Brain Injury Outcomes Division, Clinical Trial Coordinating Center
Susumu Mori, PhD	Center for Brain Imaging Science
James Tonascia, PhD	Curtis L. Melnert Professorship in Clinical Trials
Josef Coresh, MD, PhD	George W. Comstock Center for Public Health Research and Prevention
Lawrence Appel, MD, MPH	Welch Center for Prevention, Epidemiology, and Clinical Research
G. Caleb Alexander, MD, MS	Center of Excellence in Regulatory Science and Innovation; Center for Drug Safety & Effectiveness
Janet Holbrook, PhD	Center for Drug Safety & Effectiveness; Johns Hopkins Center for Clinical Trials and Evidence Synthesis
Frank C. Curriero, PhD	Spatial Science for Public Health Center
Barry Greenberg, PhD	Institute for the Prevention and Treatment of Alzheimer's Disease at Johns Hopkins
Ellen MacKenzie, PhD	Major Extremity Trauma Research Consortium (METRC)

Center Leadership	Centers of Excellence
Homayoon Farzadegan, PhD and Joseph Margolick, MD, PhD	Johns Hopkins Biological Repository
Bonni Wittstadt, MLIS	Data Services Consulting, Sheridan Libraries
Stephen N. Davis, MBBS	Institute for Clinical and Translational Research, UMD
Daniel Ford, MD, MPH	Institute for Clinical and Translational Research, JHU
Diana Gumas, MS	Core for Clinical Research Data Acquisition; Precision Medicine Analytics Platform
Neal Fedarko, PhD	Clinical Research Unit Core Laboratory
Bonnie Woods, MS/ITS, MLA	Center for Clinical Natural Language Processing
Jonathan Weiner, DrPH	Center for Population Health Information Technology
Katherine Clegg Smith, PhD	Center for Qualitative Studies in Health and Medicine
Sanjay K. Jain, MD	Center for Infection and Inflammation Imaging Research
Paul G. Auwaerter, MD, MBA	Johns Hopkins POC-IT Center
Yukari Manabe, MD	Center for Point-of-Care Tests for Sexually Transmitted Diseases
Robert Bollinger, MD, MPH	Center for Clinical Global Health Education
Cynthia Sears, MD	Microbiome Center for Immunotherapy
Alex Szalay, PhD	Institute for Data Intensive Engineering and Science
Jamie Combariza, PhD	Maryland Advanced Research Computing Center (MARCC)
Dwight Raum, BS and Paul Nagy, PhD	Johns Hopkins Medicine Technology Innovation Center
Ralph Semmel, PhD	Johns Hopkins University Applied Physics Laboratory
David Horrocks, MBA, MPH	Chesapeake Regional Information System for Our Patients (CRISP) Database

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

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TIN and TIU Overview

TIU Consult Feature: The AERO Trial

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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

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TIU Consult Highlight: Investigator Perspective

Ioan Lina, MD

Co-Investigator

The AERO Trial

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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

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Phase II Placebo-controlled Trial

1) **Study arms**: 1. Experimental – Everolimus

   2. Control – Placebo control

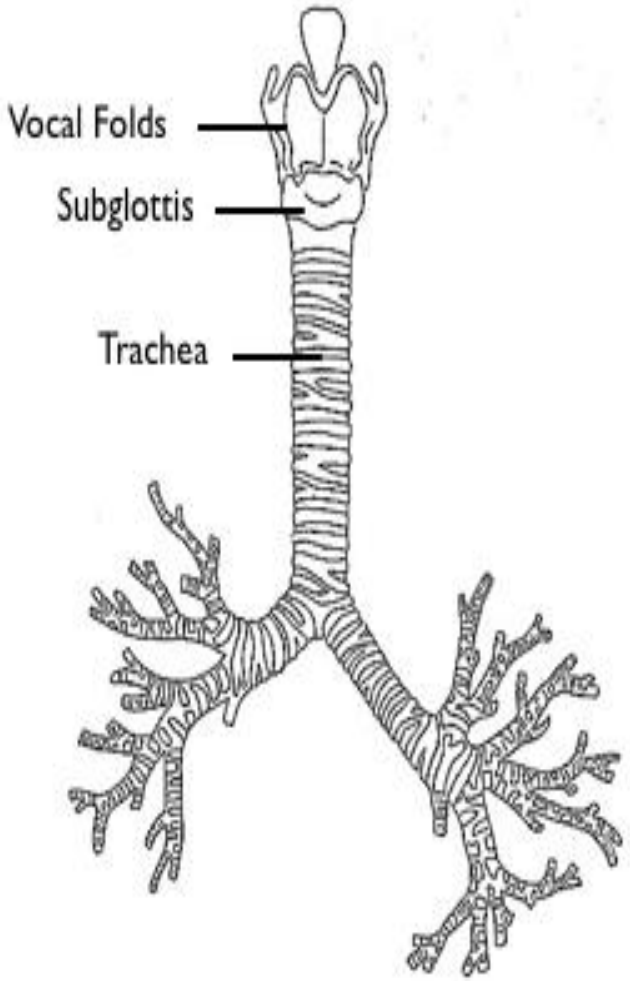
2) **Study population:** Adult laryngotracheal stenosis patients with a surgical [dilation] interval < 18 months

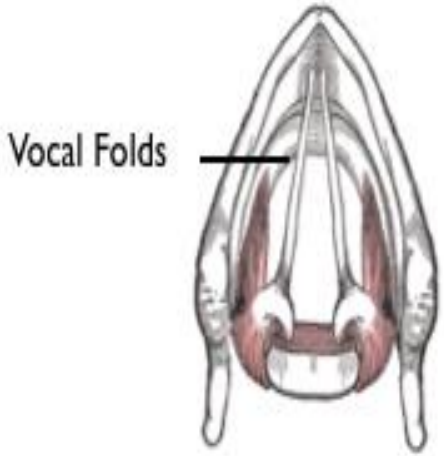
3) **Sample size:** 128 patients, 64 patients in each arm.

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)





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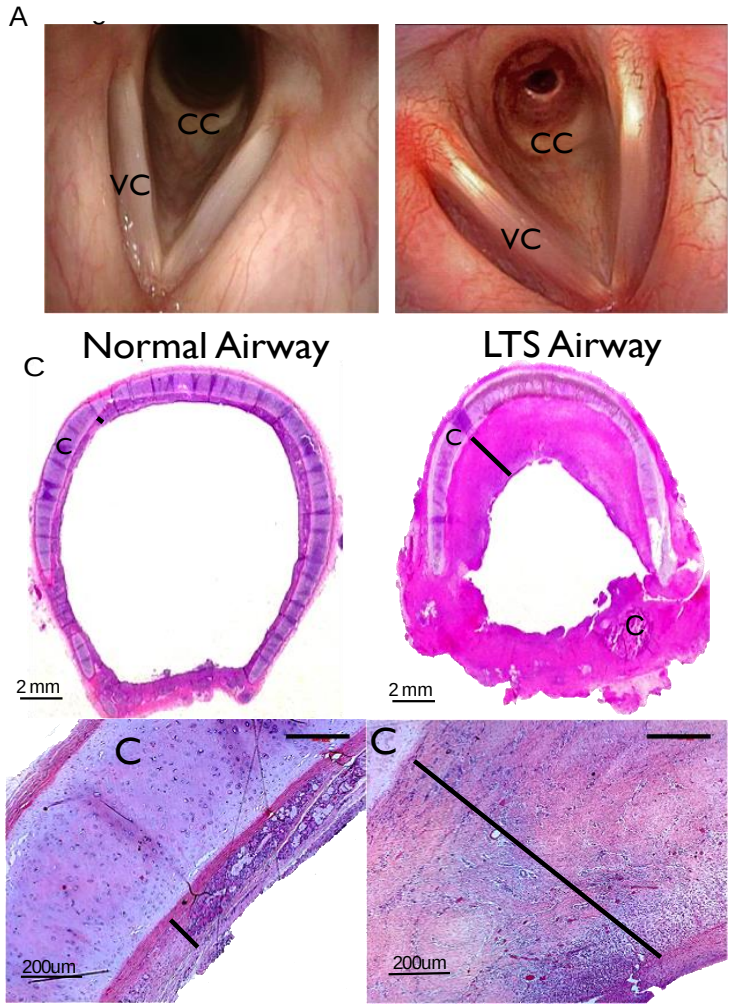
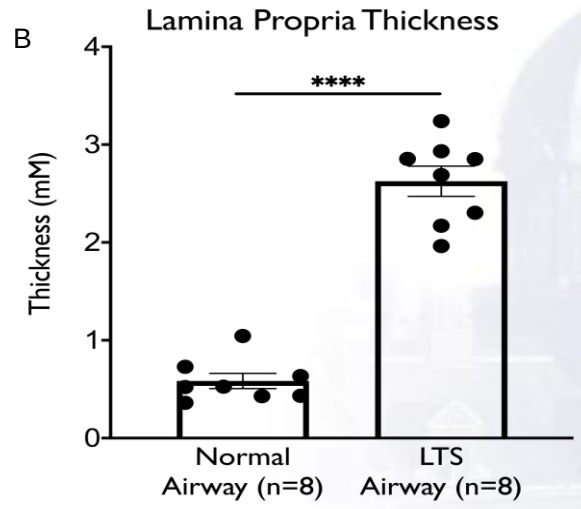
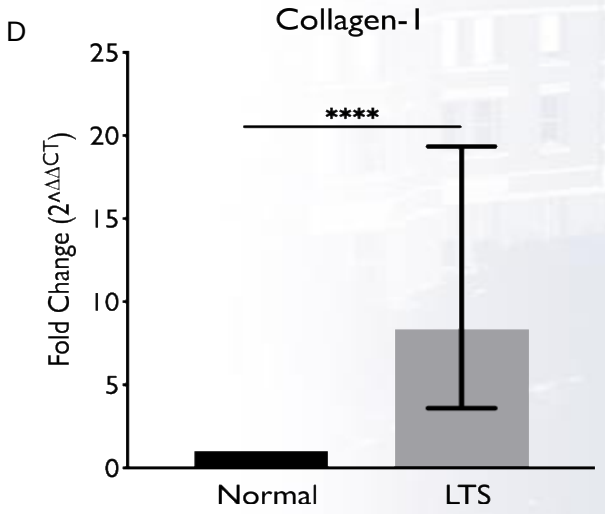
LTS is a life-threatening fibrotic disease that narrows the airway







Motz K, et al. Targeting mTOR signaling in CD4 lymphocytes with a sirolimus attenuates laryngotracheal stenosis. In Preparation.

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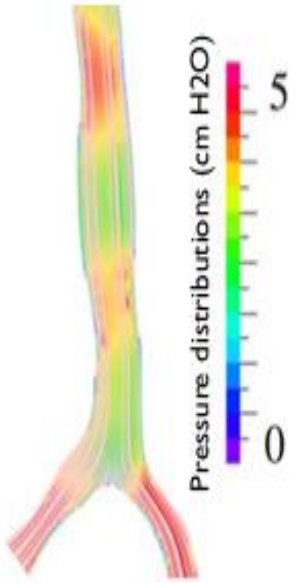
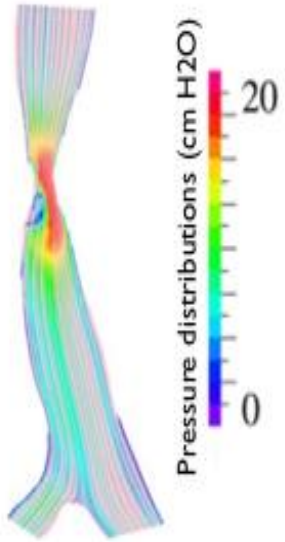
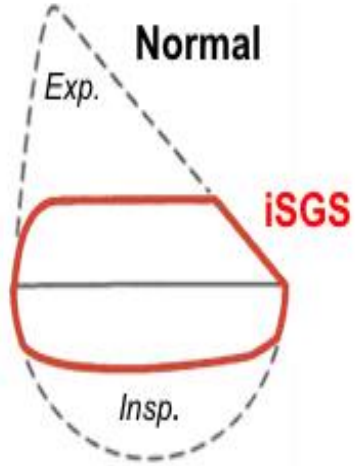
Physiologic Limitations



Normal



iSGS



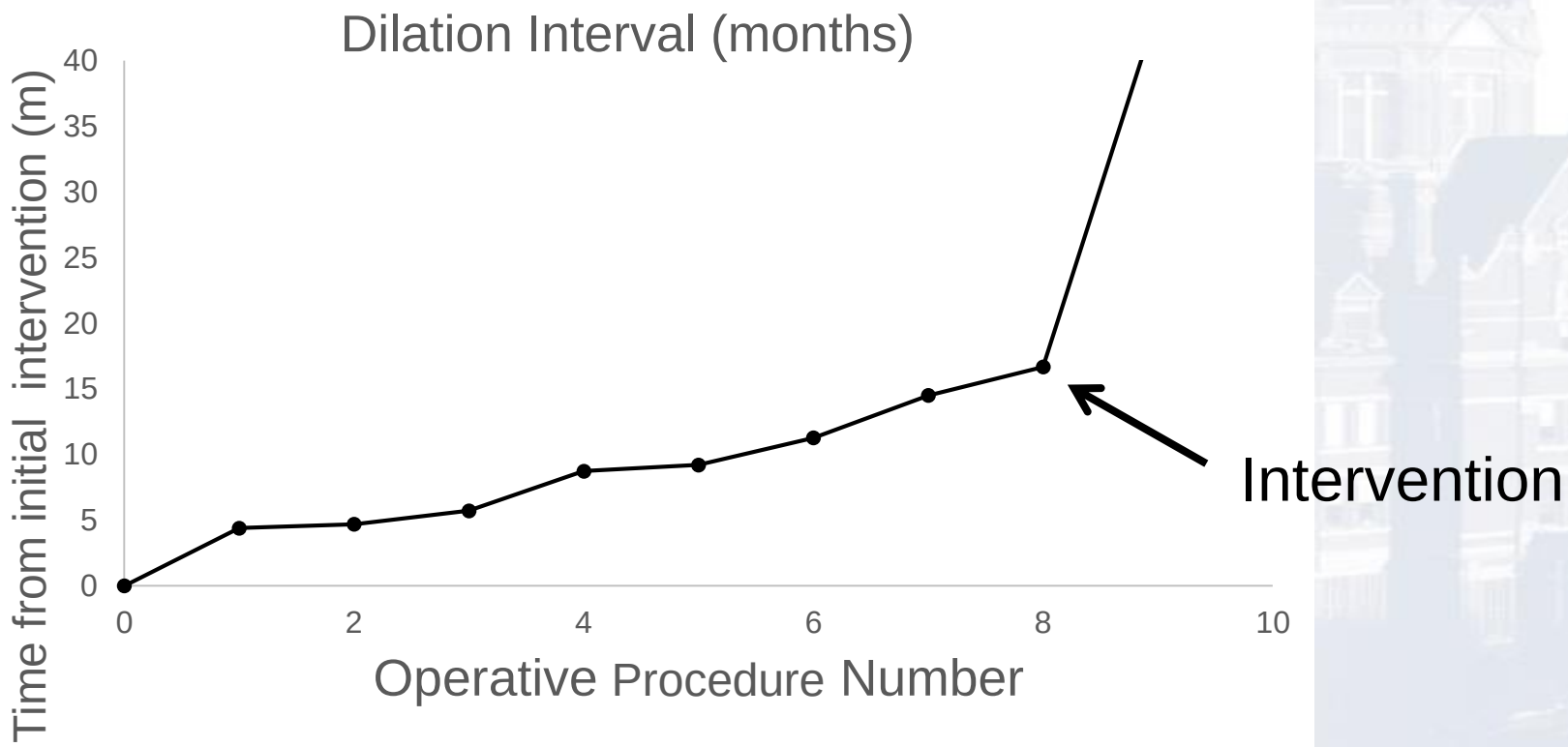
PFTs

Surgery Remains the Only Treatment Option

	Dilation	Laryngo-tracheoplasty	Cricotracheal Resection	Tracheal Resection
Total Procedures	298	42	28	16
Primary Procedure	91	15	10	11
Subsequent Procedure (%)	64 (70%)	5 (33%)	1 (10%)	4 (36%)
Complication	2 (1%)	14 (33%)	9 (32%)	4 (25%)
Mortality	0	0	1 (4%)	2 (13%)

Herrington HC, Weber SM, Anderson PE. Modern Management of Laryngotracheal Stenosis. Laryngoscope. 2006;116:1553-7.

Endoscopic Dilation is a Common Surgery Usually with a Consistent Time Interval



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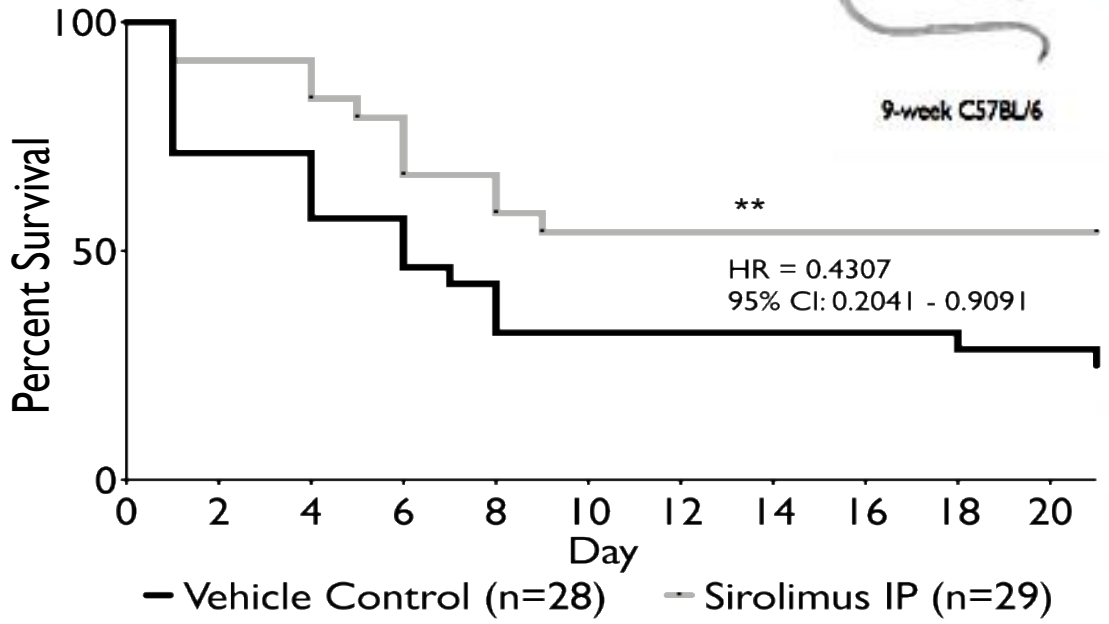
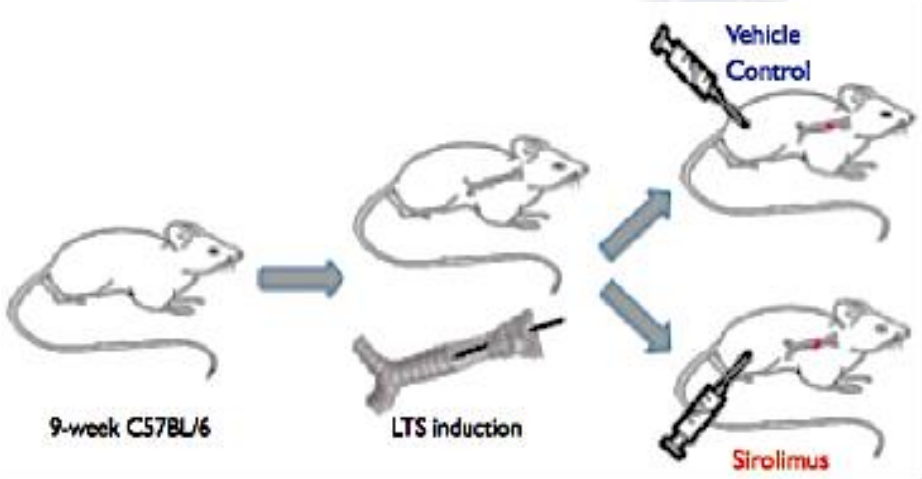
mTOR Inhibition Improves Survival in LTS Mice





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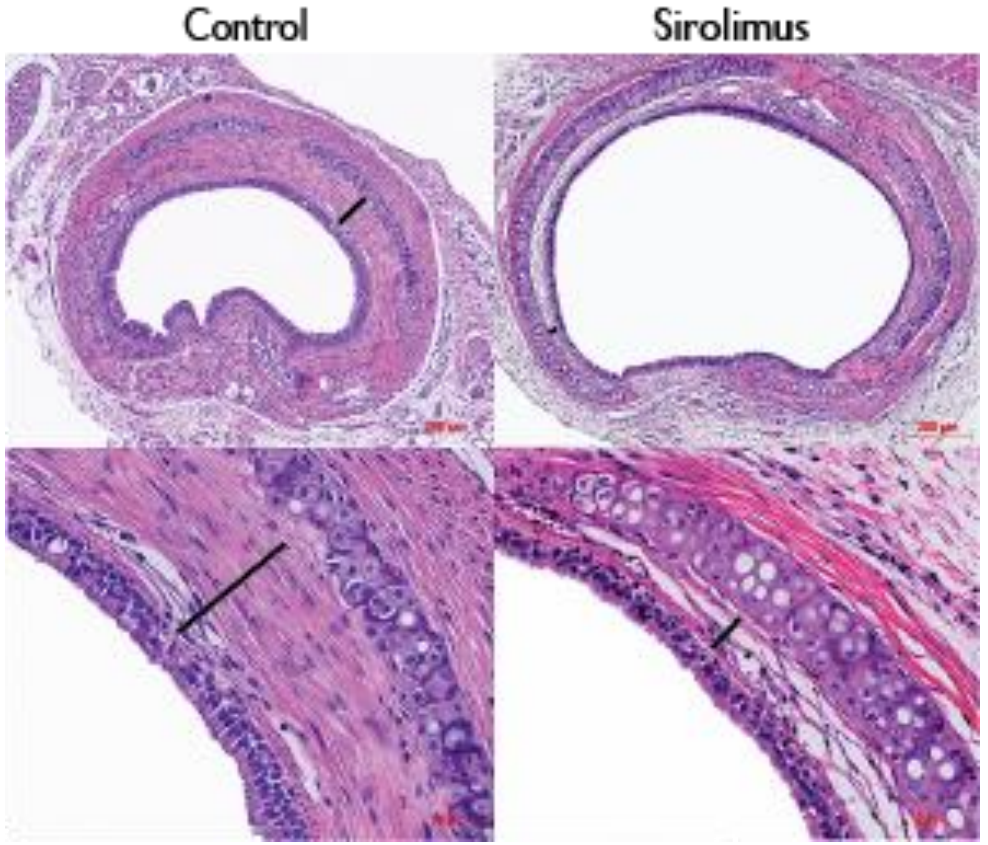
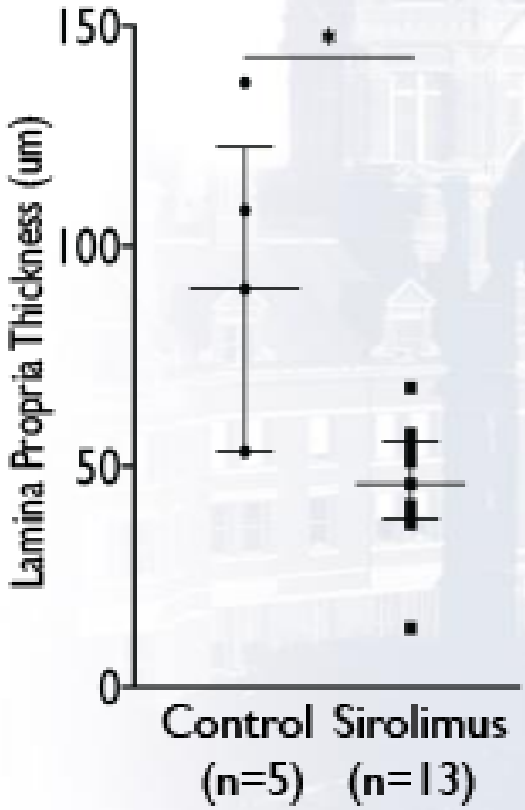
mTOR Inhibition Decreases Tracheal Lamina Propria Fibrosis at 21 days





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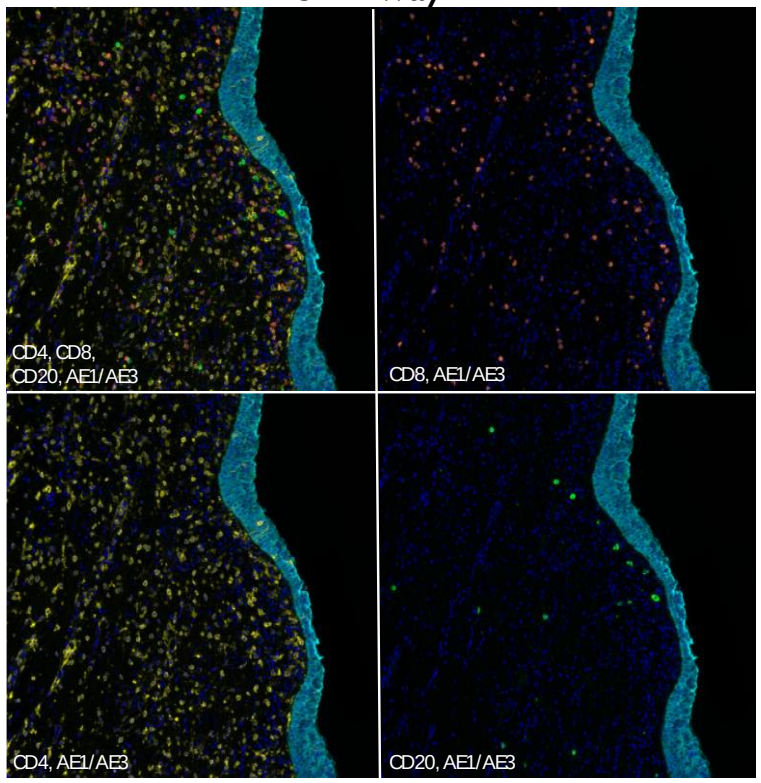
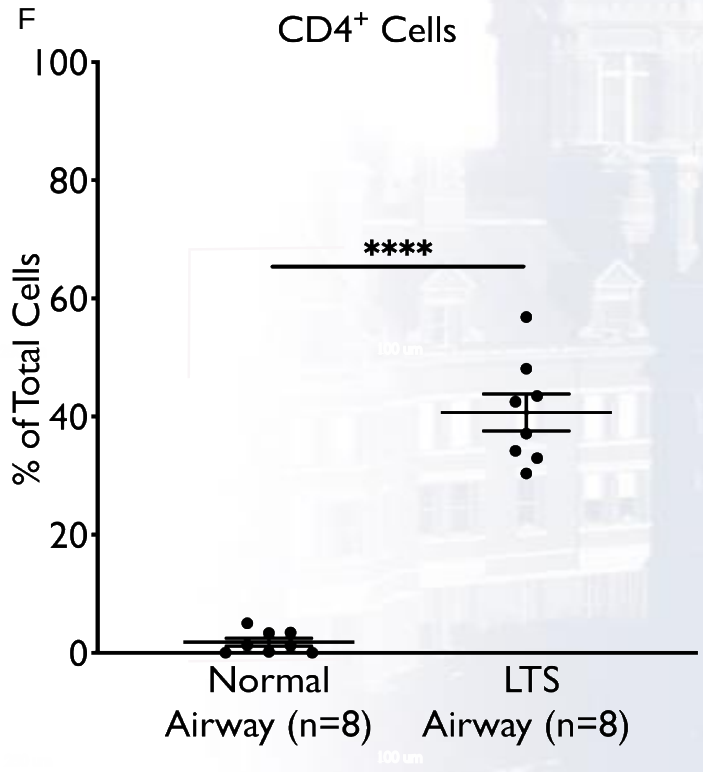
Human LTS is a CD4 mediated disease

E



CD4 = Yellow, CD8 = Orange,
CD20 = Green AE1/AE3 (Cytokeratin) = Light Blue

F



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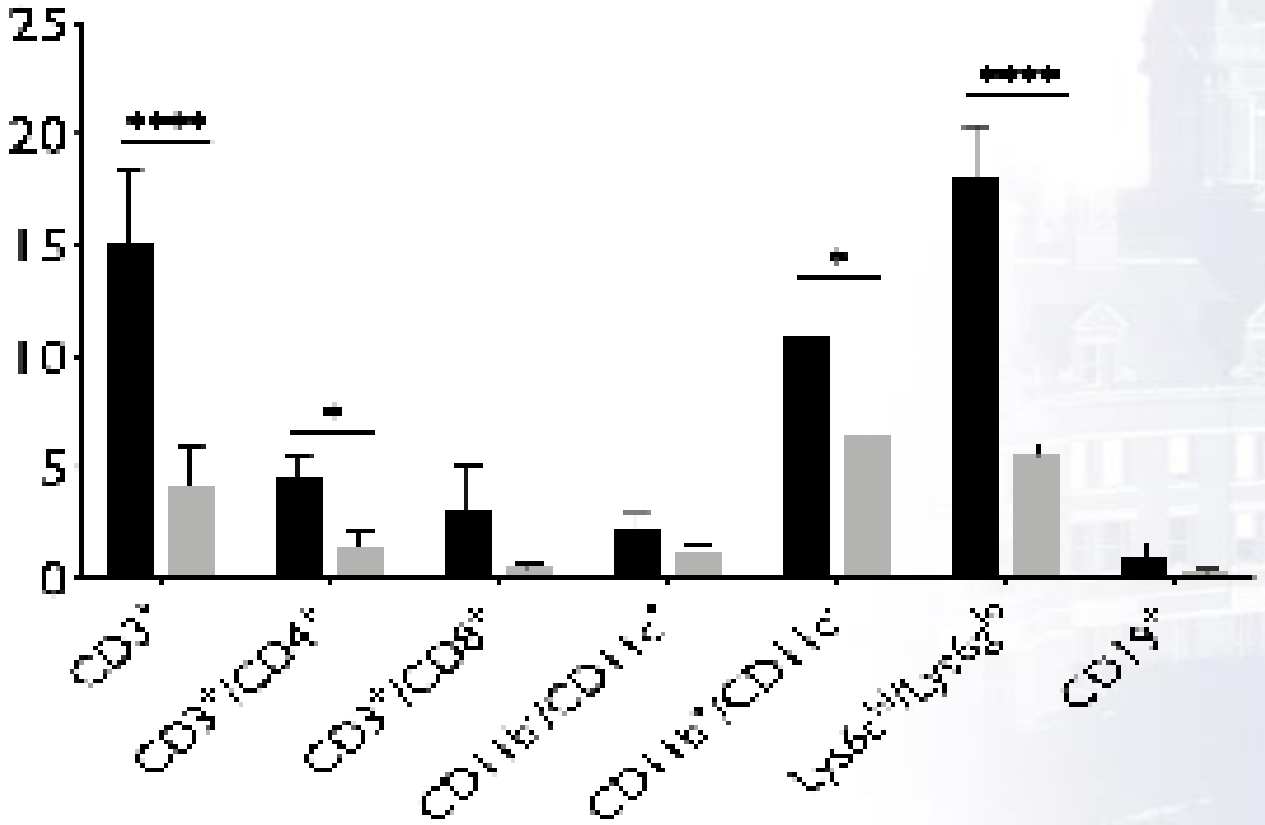
mTOR Inhibition Reduces CD4+ T-cells and Macophages



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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

YEAR	TOTAL NUMBER OF PROCEDURES	NEW PATIENTS	TOTAL PATIENTS	UNIQUE PATIENTS W/ SEVERE DISEASE
2014-15	88	43	58	17
2015-16	81	39	54	22
2016-17	91	43	64	29
2017-18	126	64	101	40
2018-19	131	51	94	40
2019-20	113	45	91	36
TOTALS	**630**	**285**	**462**	**184**

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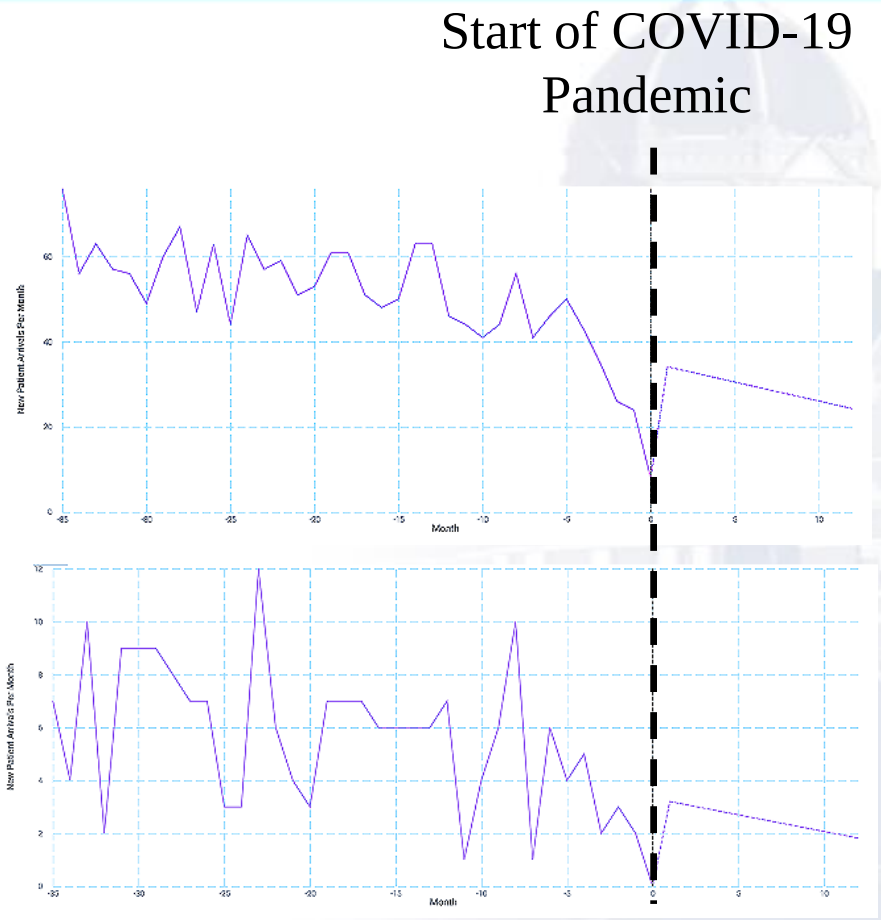
TriNetX: Patients treated for LTS

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)



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Patient-Centered Clinical Trial Design

The world's largest support community for patients with idiopathic subglottic stenosis

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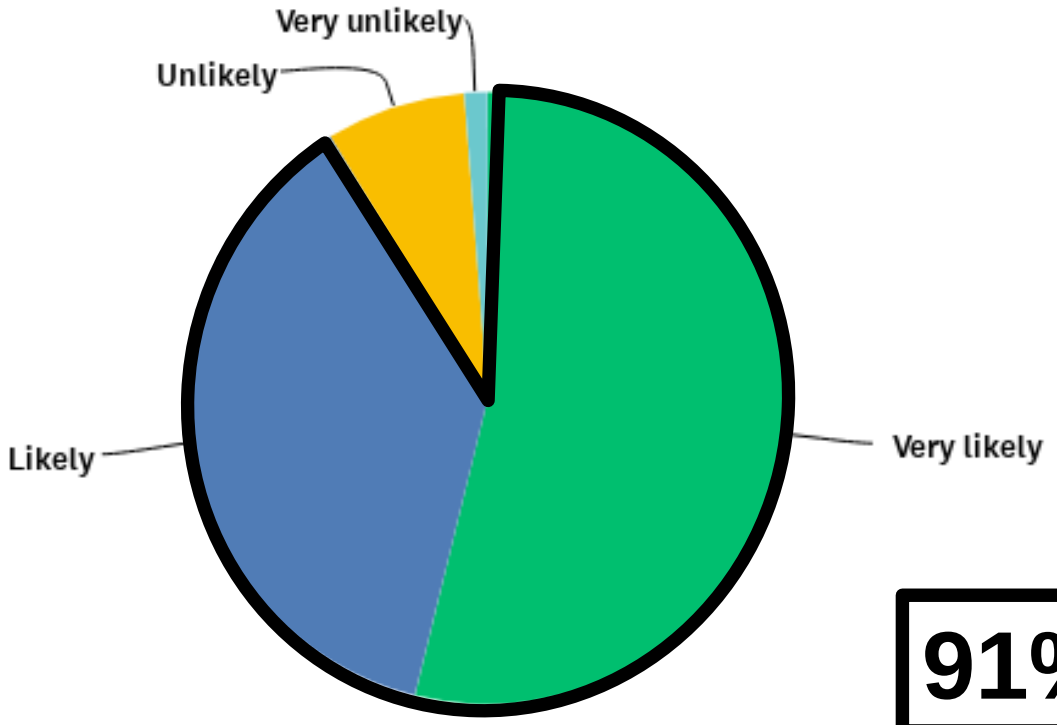
Survey Results from Patient Group

Q1: Willing to enroll in clinical trial?



91%

Answered: 323 Skipped: 0

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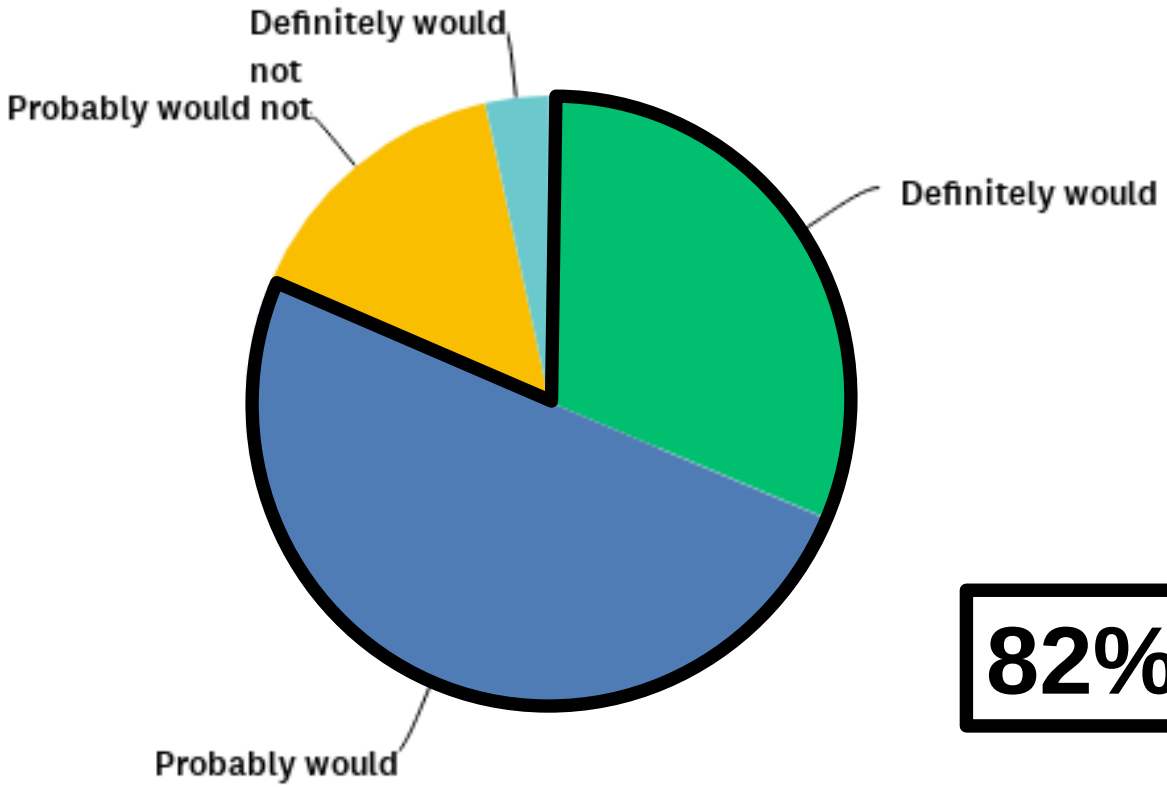
Survey Results from Patient Group

Q2: Willing to travel 200 miles for 6 visits?



82%

Answered: 323 Skipped: 0

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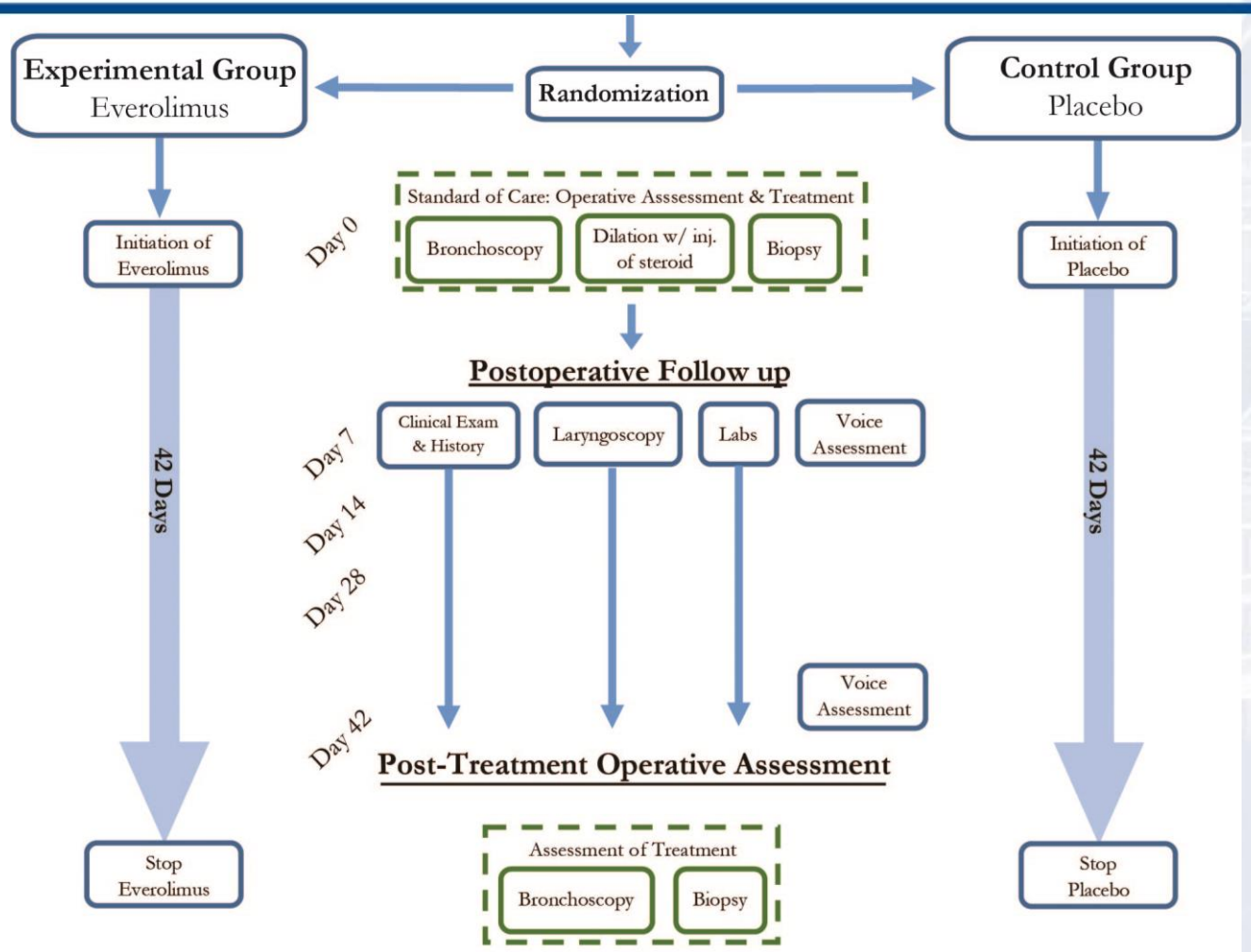
Study Design



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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/ or email ictr@jhmi.edu

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TIU and TIN Overview

Questions?

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Thank you!

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