Empowering Embedded Pragmatic RCTs in the Vanderbilt Learning Health System

Sunil Kripalani, MD, MSc, SFHM, FACP

Professor of Medicine
Division of General Internal Medicine and Public Health
Section of Hospital Medicine
Director, Center for Health Services Research
Director, Center for Clinical Quality and Implementation Research

sunil.kripalani@vumc.org
@Kripalani_Sunil
@VUMCLHS

VANDERBILT UNIVERSITY
MEDICAL CENTER

Objectives

1. Describe the organizational structures in place to support a learning health system at Vanderbilt
2. Detail the CTSA Learning Healthcare Platform model for supporting embedded pragmatic clinical trials
3. Provide several examples of supported pragmatic RCTs across a range of disciplines

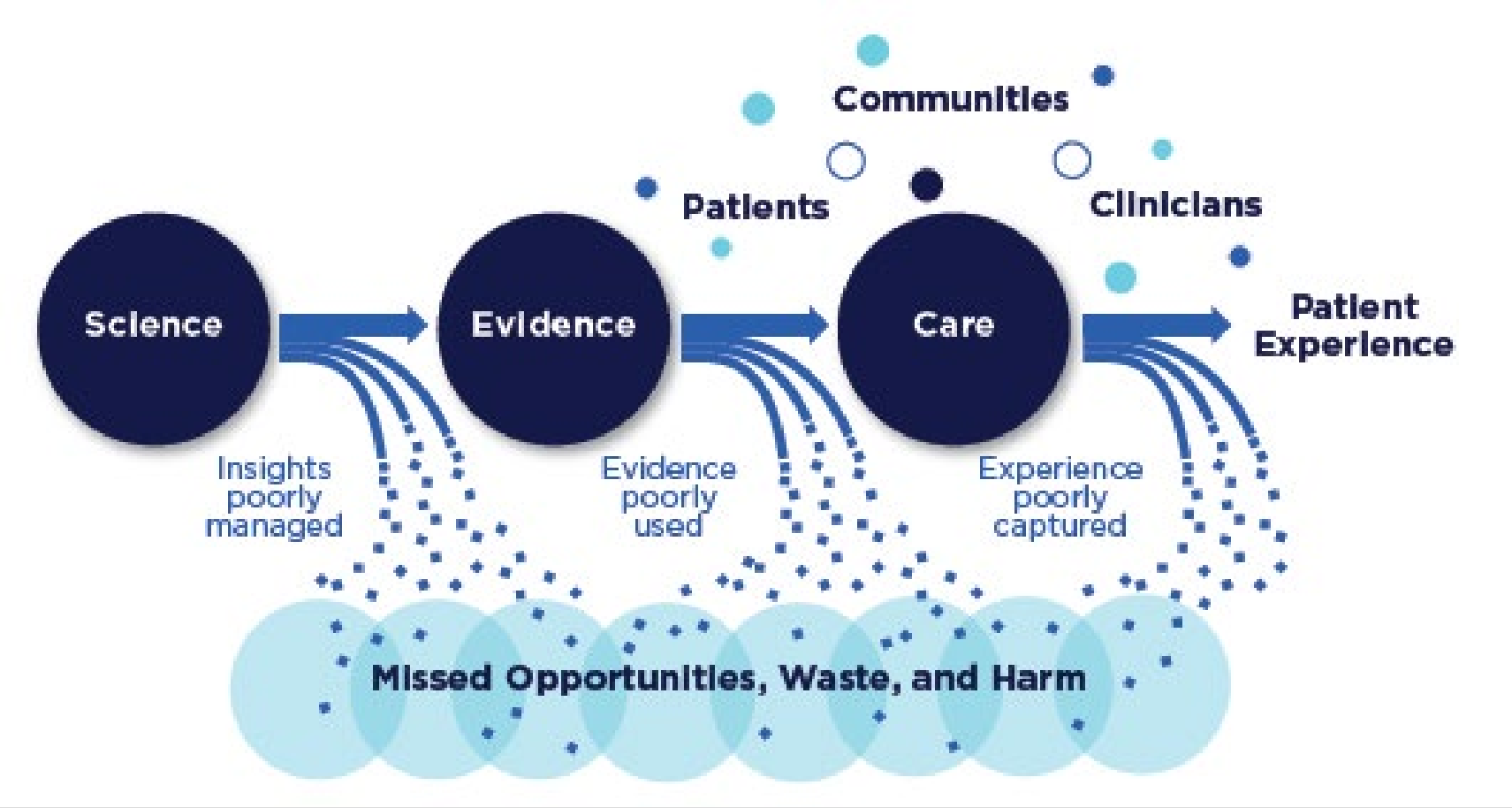
Disclosures and Funding Acknowledgements

- Dr. Kripalani has no relevant conflicts of interest to disclose.

- Learning Healthcare Platform: Vanderbilt Institute for Clinical and Translational Research (VICTR) under CTSA award UL1 TR002243 from NIH/NCATS
- Vanderbilt Center for Health Services Research and Center for Clinical Quality and Implementation Research: Institute for Medicine and Public Health
- Training programs:
  - National VA Quality Scholars Program
  - Vanderbilt Scholars in T4 Translational Research (V-STTaR): NIH/NHLBI K12 HL137943
  - Learning Health System Scholar Program at Vanderbilt: AHRQ/PCORI K12 HS026395
  - Patient/ pRactice Outcomes and Research in Effectiveness and Systems Science (PROgRESS): AHRQ T32 HS026122

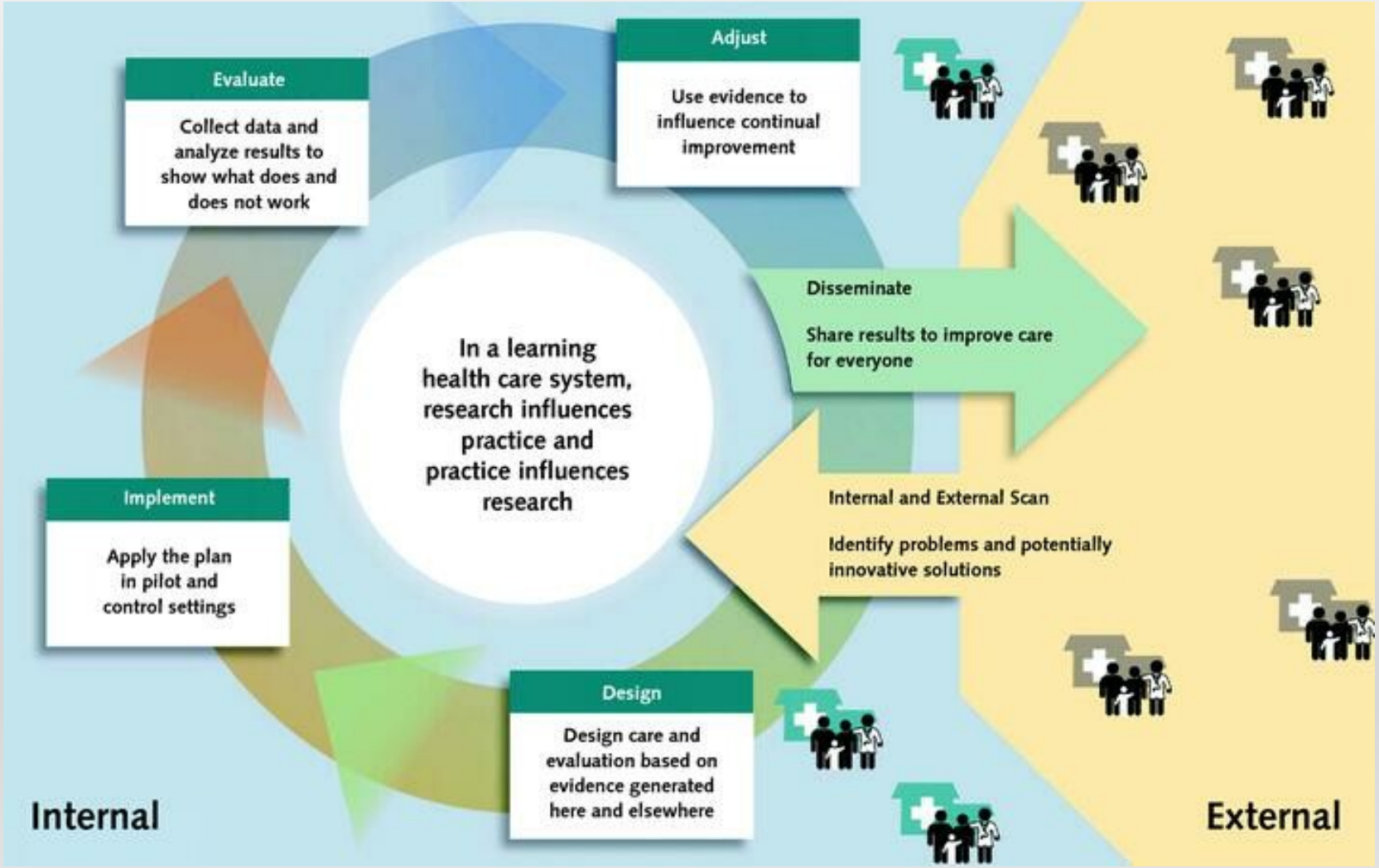
VANDERBILT UNIVERSITY MEDICAL CENTER

Traditional Approach: One-Way Pipeline from Scientific Discovery to Practice



Institute of Medicine 2013

Implementing the Learning Health System: From Concept to Action



Greene 2012

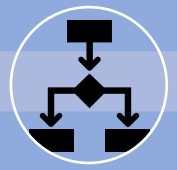
Continuous Learning Health System

- Science and Informatics
  - Real-time access to knowledge
  - Digital capture of the care experience
- Patient-Clinician Partnerships
  - Engaged, empowered patients
- Incentives
  - Incentives aligned for value
  - Full transparency
- Culture
  - Leadership-instilled culture of learning
  - Supportive system competencies

VUMC Learning Health Ecosystem

Quality Improvement

- Quality, Safety, and Risk Prevention (QSRP)
- Nursing Magnet Program
- Quality Leaders Program
- QI projects in Medicine and Nursing



Effectiveness Research

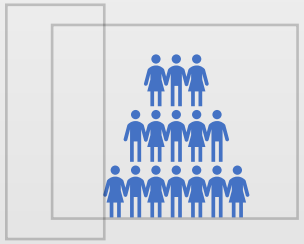
- Vanderbilt Institute for Clinical and Translational Research (VICTR) Pragmatic Trials Platform
- Center for Health Services Research
- Research Networks (STAR, HOMERuN)

Dissemination and Implementation Science

- Center for Clinical Quality & Implementation Research
- Vanderbilt Implementation and Quality Improvement (VIQI) Core
- Dissemination Core

Informatics	• Vanderbilt Clinical Informatics Center (V-CLIC) • Research Informatics (REDCap, Research Derivative)	• Enterprise Analytics • Vanderbilt Anesthesiology and Perioperative Informatics Research (VAPIR)
Stakeholder Engagement	• Patient and Family Advisory Council • Learning Healthcare Steering Committee	• Community Engaged Research Core (CERC)
D&I in Practice	• Clinical Advisory Committees, Adult & Pediatric • Clinical Decision Support	• Office of Population Health • Vanderbilt Health Affiliated Network (VHAN)
Training	• VA and Vanderbilt Quality Scholars • AHRQ T32 in Health Services Research	• AHRQ/PCORI K12 in Learning Health System Science • NIH/NHLBI K12 in Implementation Science

Vanderbilt Center for Health Services Research

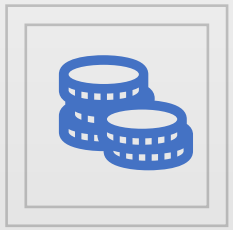


>160

- Engages more than 160 faculty from 14 departments and 3 schools

500

- Faculty involved in more than 500 publications annually

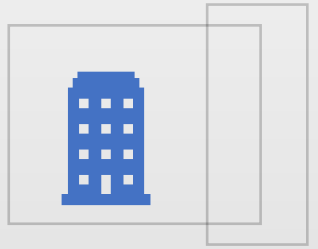


$50M

- Faculty PIs on approximately $50 million in annual funding (NIH, PCORI, CMS, Industry, etc)

Trainees

- Support ~30 post-doctoral research fellows and junior faculty in funded training programs



40K

- More than 40,000 square feet

VANDERBILT UNIVERSITY MEDICAL CENTER

CHSR Supported Centers (selected)

- Center for Clinical Quality and Implementation Research (Kripalani)
- Center for Surgical Quality and Outcomes Research (Penson)
- Center for Health Behavior and Health Education (Elasy, Mayberry)
- Center for Effective Health Communication (Cavanaugh)
- Center for Research and Innovation in Systems Safety (Weinger)
- Center for Quality Aging (Simmons)
- Center for Emergency Care Research and Innovation (Collins, Self)
- Center for Critical Illness, Brain Dysfunction and Survivorship (Ely, Pandharipande)
- Women's Health Research (Velez-Edwards)
- Center for Child Health Policy (Patrick)

VANDERBILT UNIVERSITY
MEDICAL CENTER

Center for Clinical Quality and Implementation Research

- Designs and leads innovative research and training initiatives focused on the **sciences of improvement**, **implementation**, and **dissemination** in order to maximize individual and community health and well-being through advancing the **quality and value of health care delivery**.
- 35 affiliated interdisciplinary faculty
- Helps support 23 current trainees through funded post-doctoral research fellowships and K12 programs
- Education: MPH program courses, weekly scholarly series, annual symposium

VANDERBILT UNIVERSITY
MEDICAL CENTER

CCQIR Extramural Research Examples

Tailored dissemination and implementation of emergency care clinical decision support to improve emergency department disposition	Putting Telehealth to the Test: Diabetes Prevention Program (DPP)	SHED-Meds: Medication Deprescribing	Quality Improvement Collaborative for COVID-19 in Middle TN Nursing Homes
• NIH/NHLBI, R01 award • Implement and test effectiveness of clinical decision support tool to identify low-risk heart failure patients for potential discharge	• NIH/NIDDK, R01 award • Adapt and evaluate telehealth delivery of VUMC HealthPlus employee diabetes prevention program	• NIH/NIA, R01 award • Evaluate deprescribing protocol for elderly patients with polypharmacy	• CMS Civil Monetary Penalties Program • Engage 50+ nursing homes in mentored quality improvement activities to prevent and control COVID-19

CHSR and CCQIR in the Learning Health System

- One of three strategic priorities for growth
- Partner with high-priority operational initiatives
  - Ex: Vanderbilt Discharge and Transitions Initiatives, Vanderbilt Hospital at Home, Vanderbilt Familiar Faces Program
- Provide expertise in patient-centered outcomes research, comparative effectiveness research, implementation science, health communication, health behavior change, mixed-methods evaluation, survey research, qualitative research, community and stakeholder engagement
- Evaluate what interventions work best, for whom, and in what settings?

Career Development Programs in Implementation Research and Learning Health Systems

V-STTaR K12
Vanderbilt Scholars in T4 Translational Research

NIH/NHLBI
4 Faculty, 2 Alumni
Kripalani | Roumie

VA Quality Scholars Program

VA Health System
8 Scholars, 55 Alum
Dittus

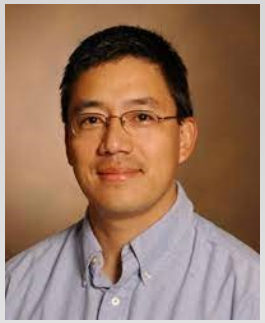
LHSS K12
Vanderbilt Learning Health System Scholars

AHRQ/PCORI
4 Faculty, 4 Alumni
Roumie | Rothman

PROgRESS T32
Vanderbilt Patient / pRactice Outcomes Research in Effectiveness and Systems Science

AHRQ
7 Postdocs, 7 Alum
Roumie | Grijalva

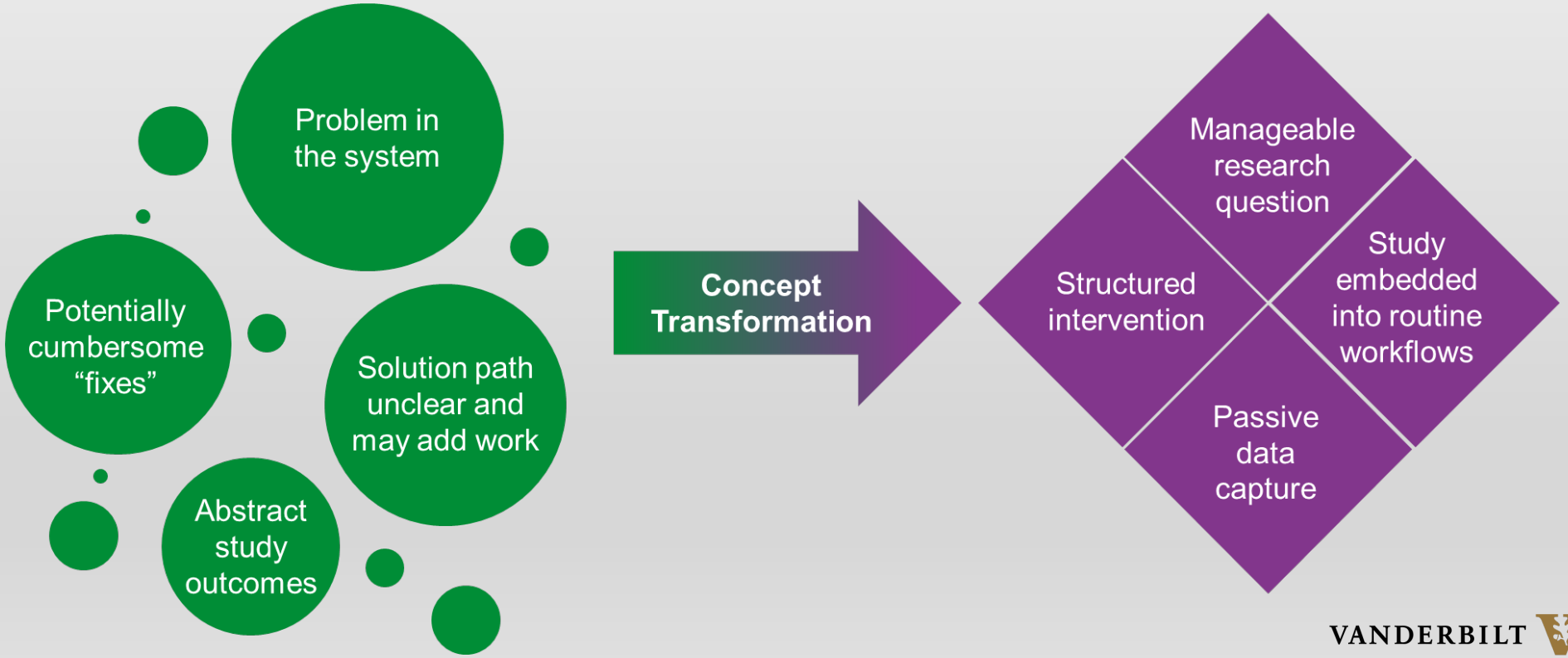




VANDERBILT UNIVERSITY MEDICAL CENTER

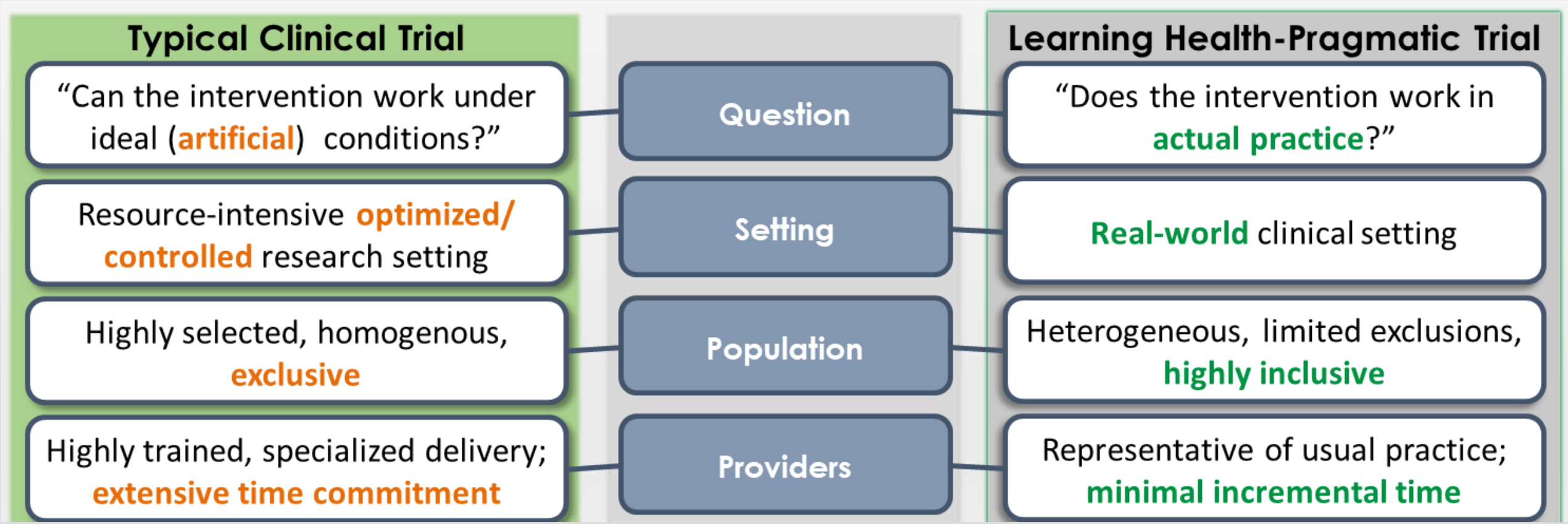
Vanderbilt Learning Healthcare Pragmatic Trials Platform

- Generate practice-based evidence for intervention effectiveness
- Focused on rigorous, embedded, pragmatic clinical trials

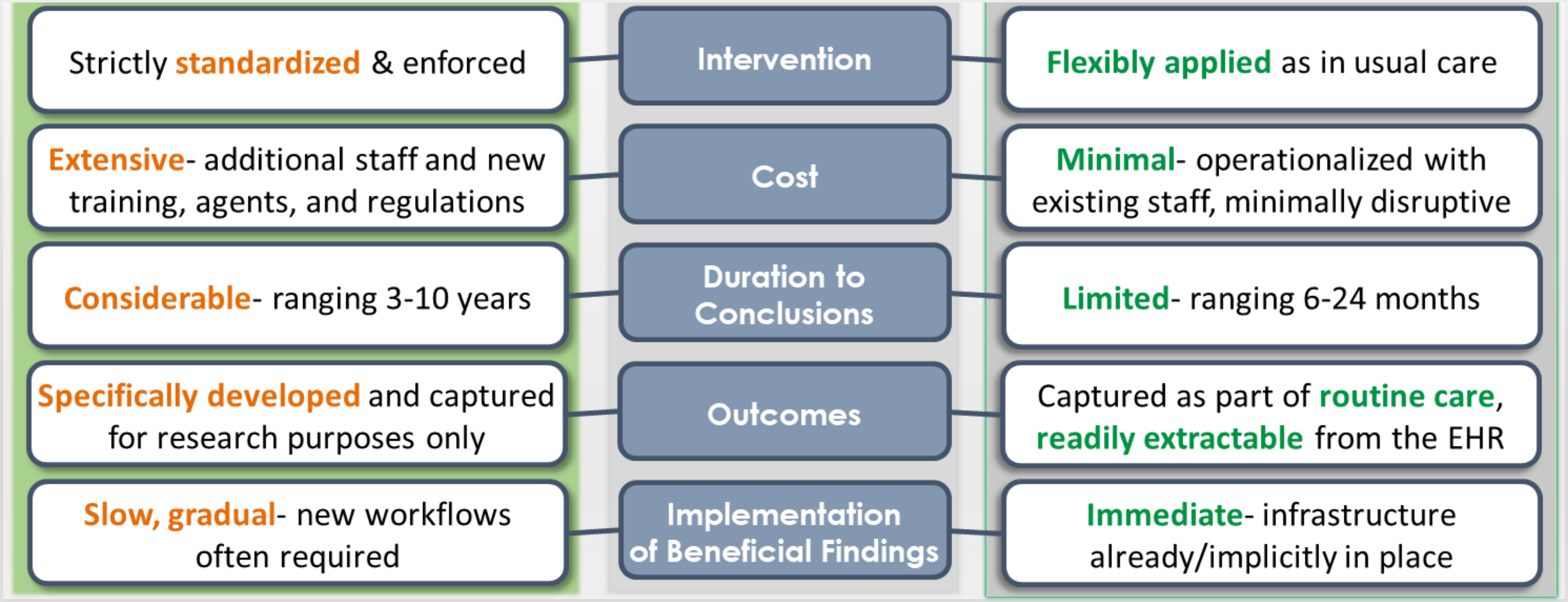


VANDERBILT UNIVERSITY MEDICAL CENTER

Typical Efficacy Trials vs. Embedded Pragmatic Effectiveness Trials

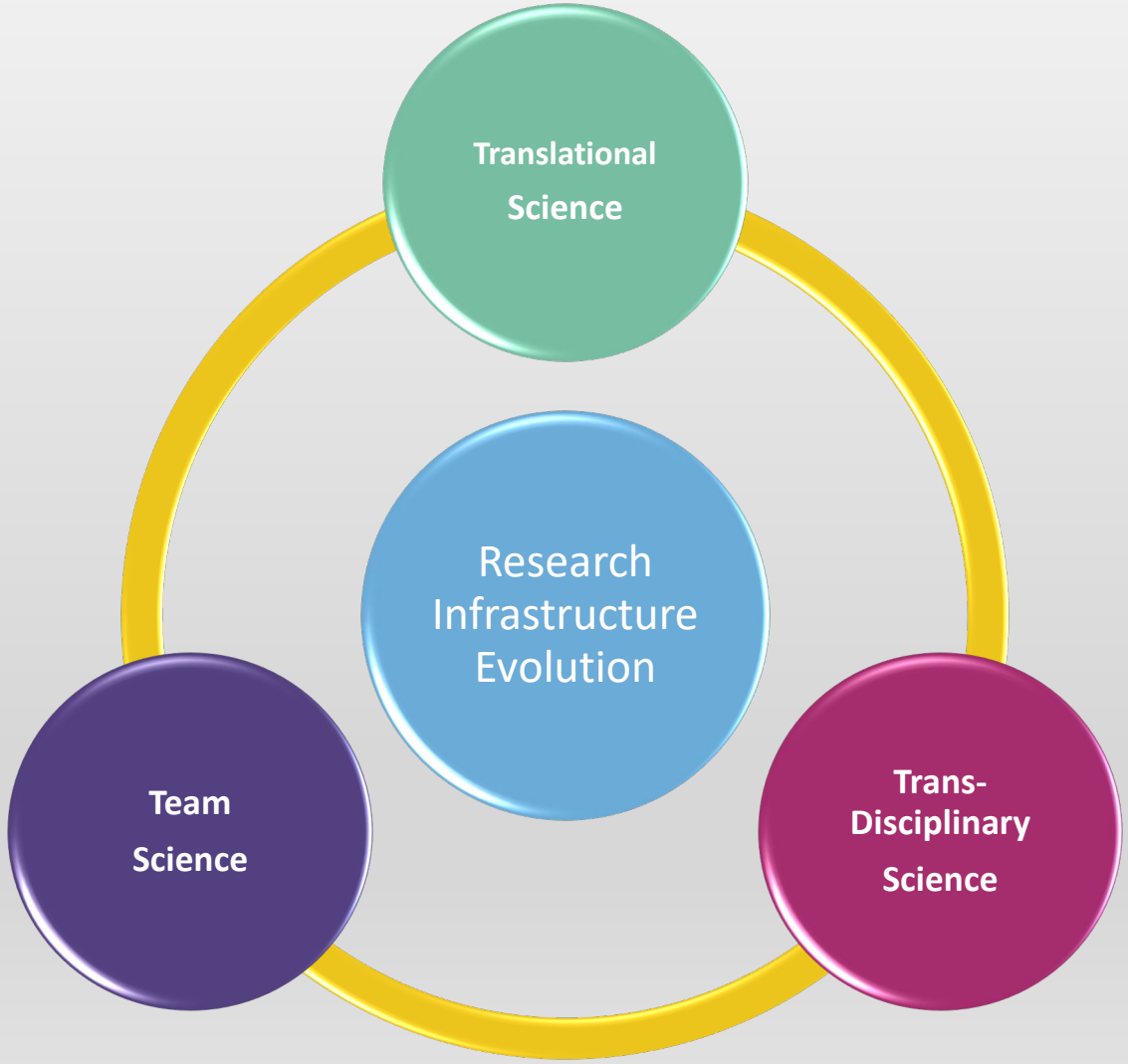


Typical Efficacy Trials vs. Embedded Pragmatic Effectiveness Trials

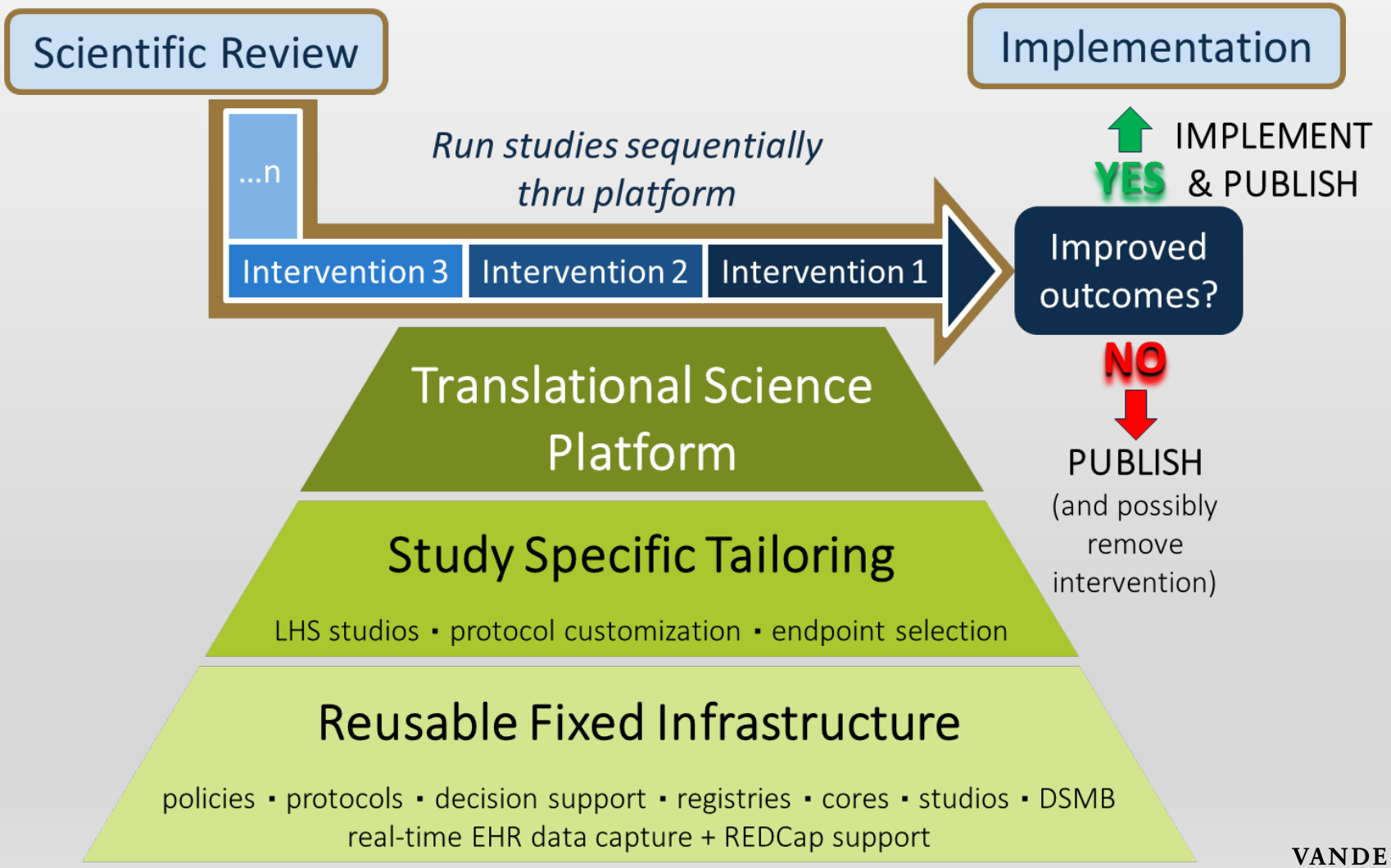


What considerations go into supporting this type of work?

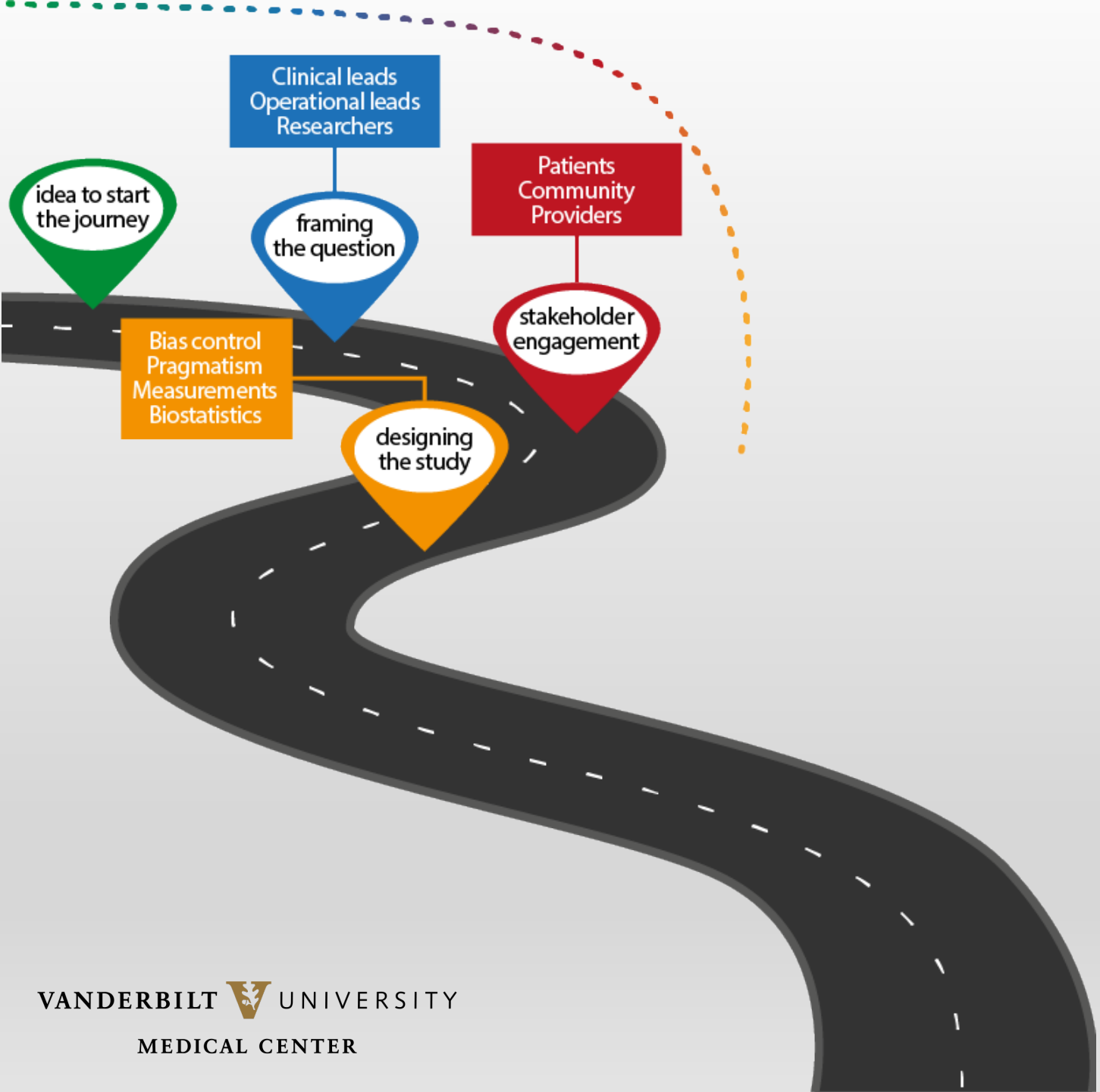
- Complex clinical questions require multi-faceted approaches
- Barriers often exist to initiating and conducting these studies
- Robust research support infrastructure can lower that activation energy
- Building those solutions requires methodical, purposeful design
- Need reusable, scalable, adaptable frameworks that promote rigor and reproducibility



Learning Healthcare in Action – The Platform



VANDERBILT UNIVERSITY MEDICAL CENTER

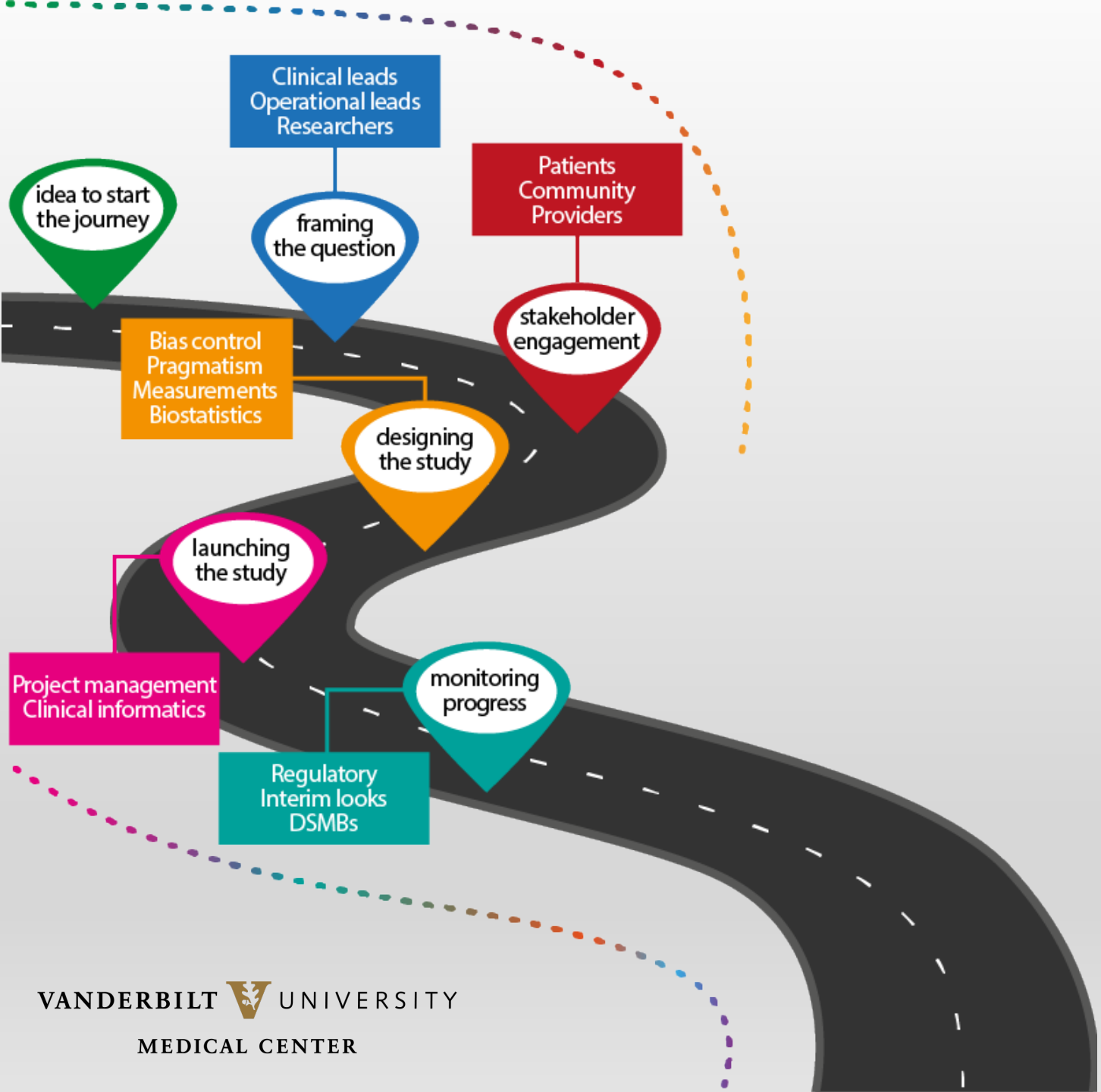


What do we offer?

- LHS discussion and brainstorming with pragmatic focus
- Identification of collaborators
- Literature/data review
- Clinical trial design
- Selection of appropriate endpoints
- Regulatory considerations and guidance
- Connection to other services as appropriate

Goal: executive summary

Adapted from Lindsell et al. Acad Med 2021



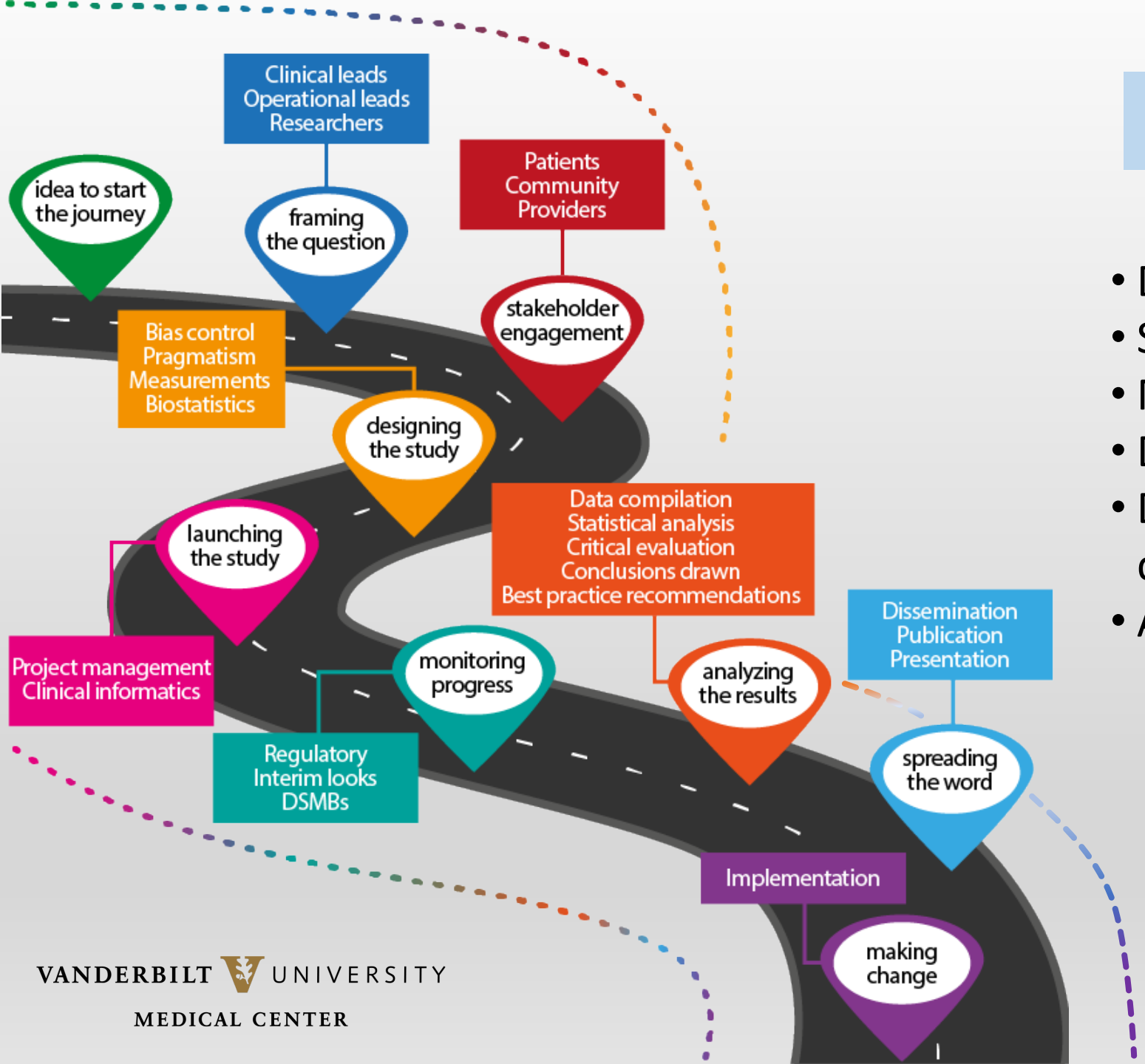
VANDERBILT UNIVERSITY MEDICAL CENTER

What do we offer?

- Project management
- Core engagement
- Studios
- Recruitment/Consent elements
- Protocol/SOP/IRB drafting
- Statistical analysis plan
- DSMB
- clincialtrials.gov registration
- Informatics consults
- Data management and IT processes

Goal: protocol and study operational plan in motion

Adapted from Lindsell et al. Acad Med 2021



What do we offer?

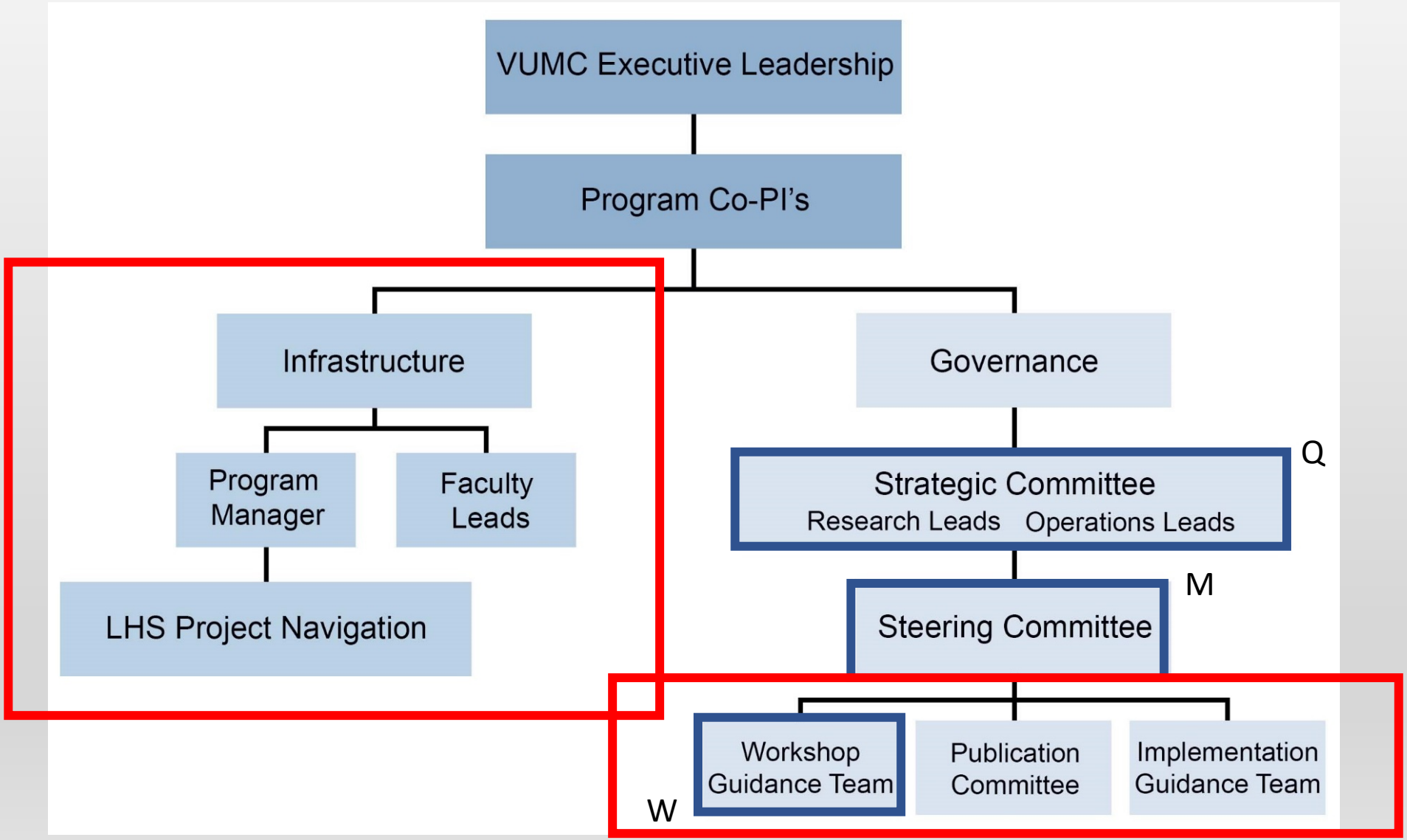
- Data management support
- Statistical analysis
- Manuscript development
- Dissemination Team engagement
- Drafting and execution of dissemination plan
- Advice on implementation?

Goal: robust, disseminated answer sufficient to guide decision to implement/de-implement

Adapted from Lindsell et al. Acad Med 2021

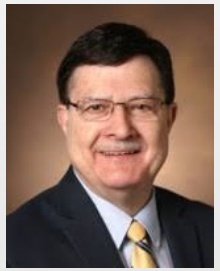
VANDERBILT UNIVERSITY MEDICAL CENTER

How is this structured at Vanderbilt?



Learning Healthcare Executive Leadership

Operations Leadership



Jim Hayman, MS, MBA
Chief Pharmacy Officer

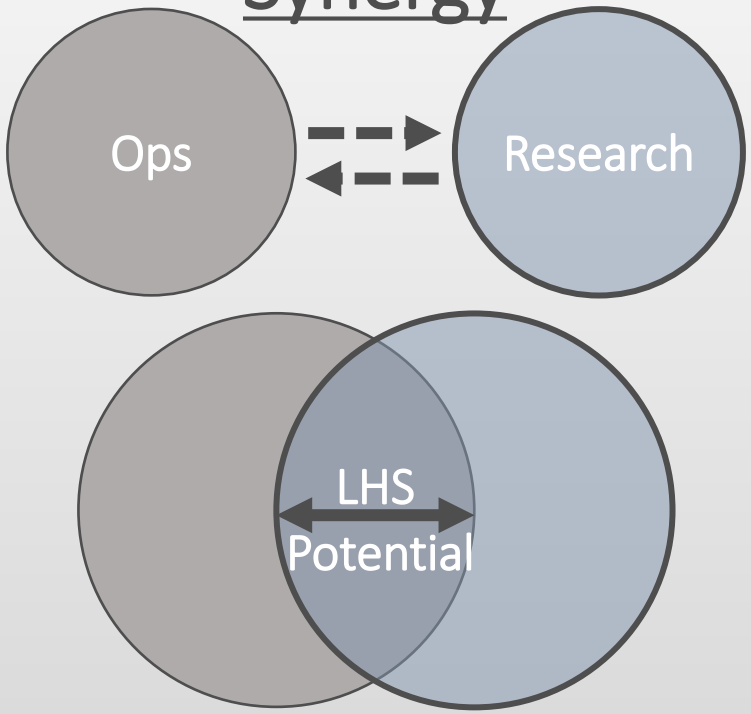
Robin Steaban, RN
Chief Nursing Officer

Thomas Nantais, MBA
Executive VP for Adult Ambulatory Operations

Shon Dwyer, RN, MBA
President of VUAH

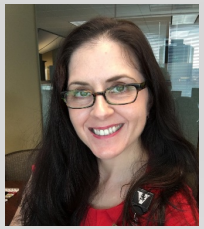
Lee Ann Liska
Chief Operating Officer

Synergy



VICTR Infrastructure Leadership

Jill Pulley, MBA
Executive Director
VICTR



Cheryl Gatto, PhD, PMP
Associate Director
VICTR

Research Leadership

Gordon Bernard, MD
Director, VICTR
Executive VP for Research

Bob Dittus, MD, MPH
Chief Innovation Officer
Senior VP, VHAN

Chris Lindsell, PhD
Director, Research Methods VICTR
Associate Director, CCQIR

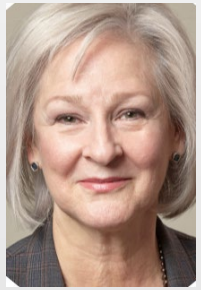
Todd Rice, MD, MSc
Director, MICU VUH
Medical Director, HRPP

Learning Healthcare – Expertise

Operational Expertise

Nursing

Ruth Kleinpell, PhD



Patti Runyan, MBA, RN, BSN

Cathy Ivory, PhD

Jay Morrison, MSN

Education

Don Moore, PhD

Philip Walker, MLIS, MSHI

Pharmacy

Autumn Zuckerman, PharmD

Quality

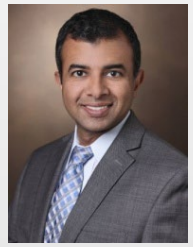
Neesha Choma, MD, MPH

Mark Bennett, MD

Jenny Slayton, RN, MSN

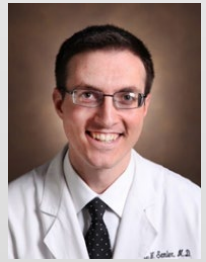
Scientific & Research Expertise

Tina Hartert, MD, MPH



Sunil Kripalani, MD, MSc

Russell Rothman, MD, MPP



Matt Semler, MD, MSCI

Wes Self, MD

Community Engagement Expertise

Consuelo Wilkins, MD, MSCI

Patrick Luther, MHS

Learning Healthcare – Expertise

Biostatistics

Frank Harrell, PhD

Sam Nwosu, MS

Cassie Hennessy, MS

Yue Gao, MS

Data & Bioinformatics

Paul Harris, PhD

Adam Wright, PhD

Robert Freundlich, MD

Marc Beller

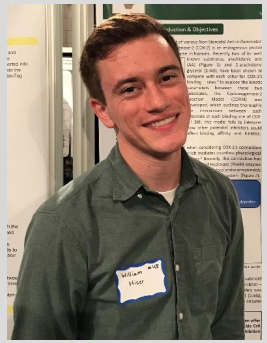
VICTR LHS Platform Support Team

Project Management

Mary Lynn Dear, PhD

Justin Siemann, PhD

HSRA



William Hiser

HSRA

Grace Van Winkle

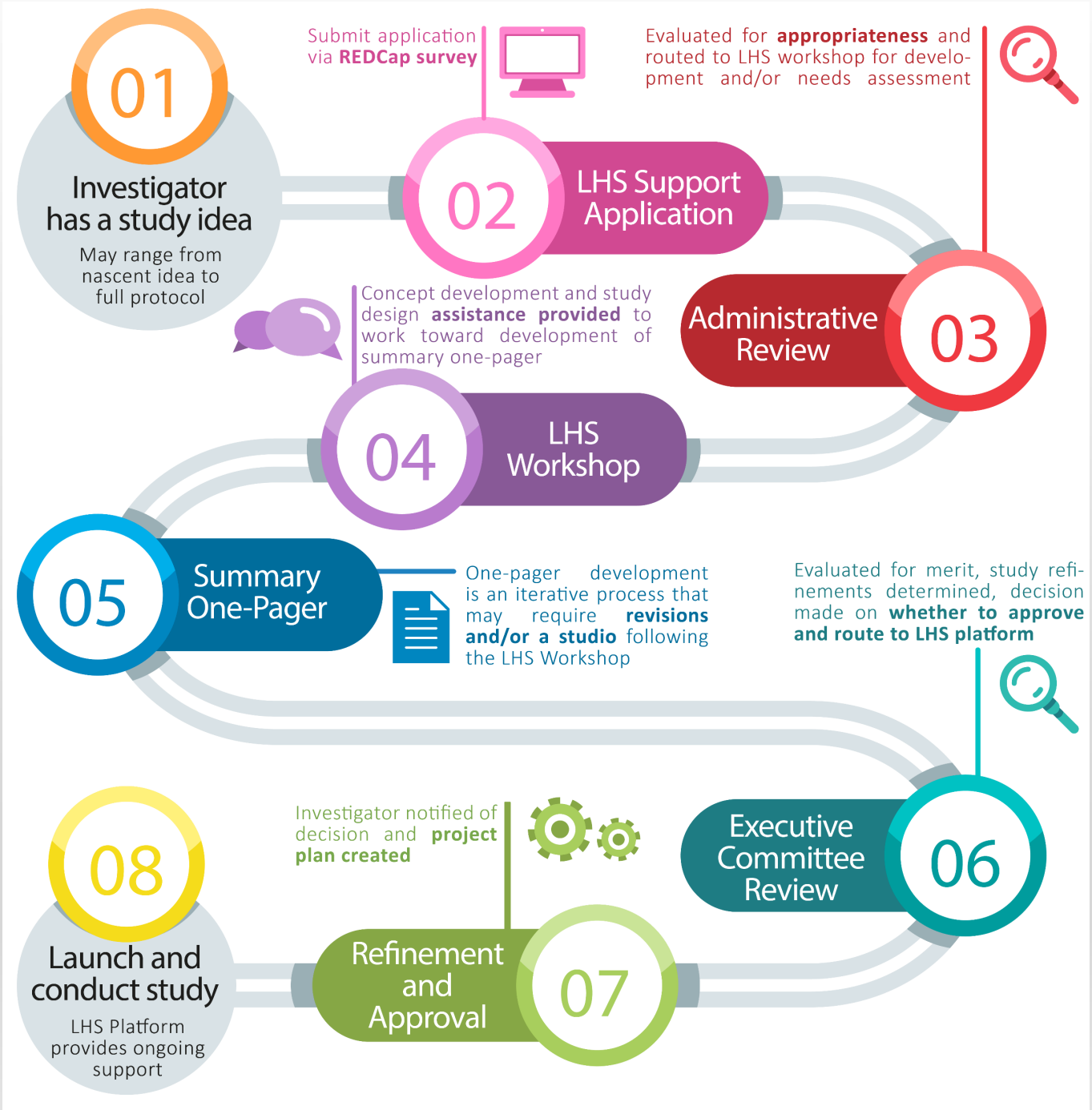
Associate Program Manager

Estefania Gibson

Stakeholder Engagement

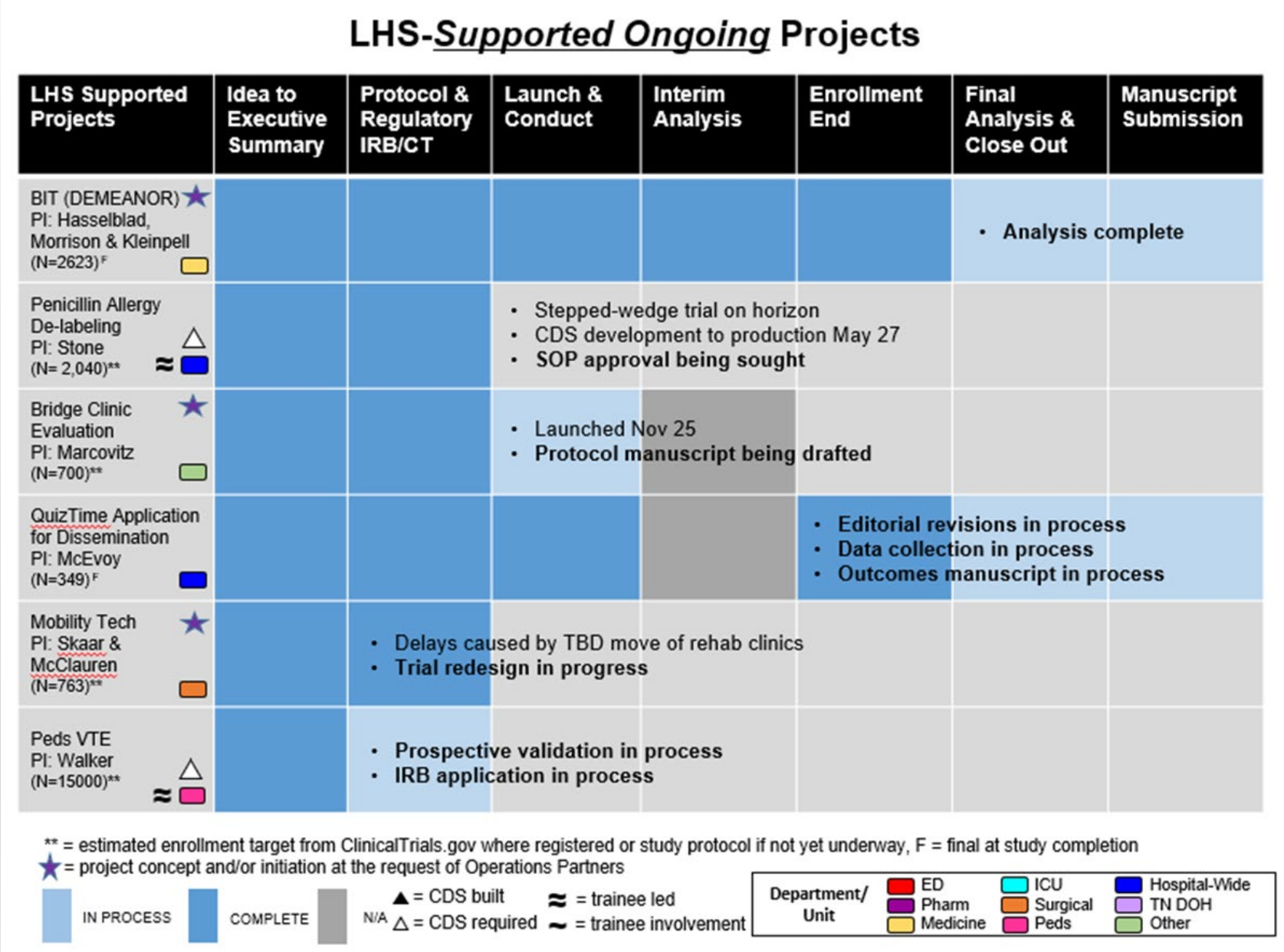
Steering Committee for the Vanderbilt Learning Healthcare System	
Research & Implementation	Executive Vice President for Research, Chief Innovation Officer, CTSA Directors, Medical Director of the Institutional Review Board, Director of Vanderbilt Coordinating Center, Director of the Center for Clinical Quality and Implementation Research, Staff Statisticians, Program Managers
Hospital Operations	President VUAH, Chief Nursing Officer, Chief Operating Officer, Chief Pharmacy Officer, Executive VP for Adult Ambulatory Operations, Sr Vice President for Health Equity, Sr Vice President for Public Health, Director of the Office for Continuing Professional Development
Clinicians	Chief of Hospital Medicine, Director of Medical ICU, Vice Chair for Research in the Department of Emergency Medicine, Cardiac Anesthesiologist, Inpatient Registered Nurse, Pharmacist
Patients & Community	Patient and Community Representatives, Members of the Community Engaged Research Core Advisory Council, Biomedical Library Director

Internal Processes: from idea to developed study



VANDERBILT UNIVERSITY MEDICAL CENTER

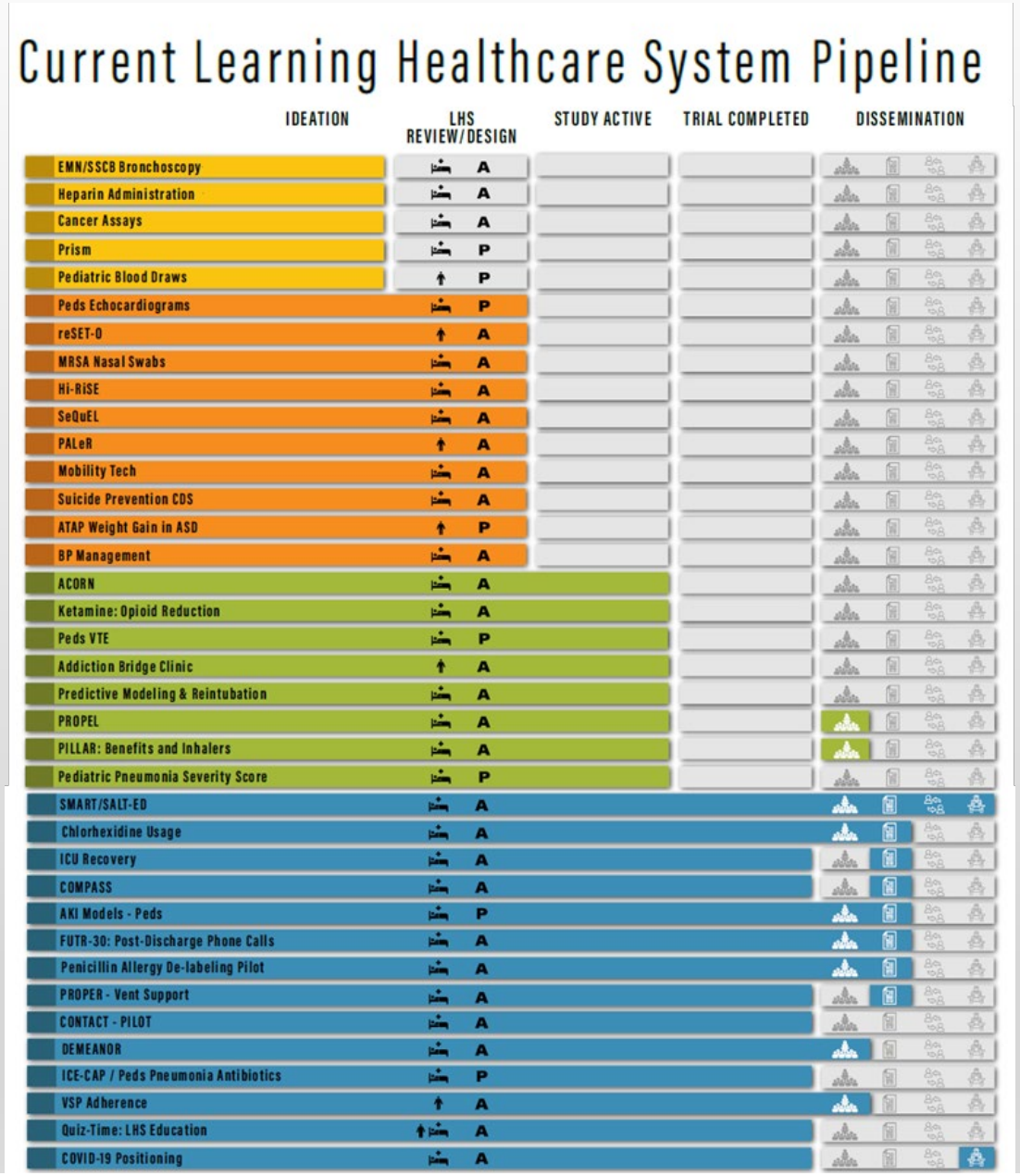
Tools: How do we track progress? – High Level RCT Steps



Tools: How do we track progress? – Life Cycle

Project					Concept Development					Pragmatic Clinical Trial									Dissemination				Implementation				
Topic	Summary	Therapeutic Area/Indication	Type of Intervention	Operations Request	Prelim Feasibility	Evidence Deep Dive	Biostats and Study Design	Biostatistician Assigned	Executive Summary	Protocol Drafted	Funding secured	IRB and CT.gov	In Conduct	Interim Analysis	Enrollment Completed	Data Lock	Analysis Complete	Publication	Consult with Dissemination Team	Internal Dissemination Plan	External Dissemination Plan	Media Engagement	BPA Recommendation	Consult with Quality	Metrics Definition	Transition to Operational Monitoring	Study Archived
SMART	Which is better: saline or lactated ringers for routine fluid administration?	Fluid Use - ICU & ED	Comparative Therapeutic		●	●	●	LW	●	●	●	●	●	●	●	●	●	NEJM	●	●	●	●	●	●	●	●	●
FUTR-30	Does a post-discharge follow-up phone call reduce readmissions and improve patient satisfaction?	Readmissions - Gen Med	Intervention Value Assessment	●	●	●	●	HD	●	●	●	●	●	●	●	●	●	Medical Care									
QuizTime	Does an on-the-go educational platform (QuizTime) provide better dissemination and uptake of information than other approaches after results from a study are released?	VUH	New Program Value Assessment (Education)		●	●	●	CL	⊗	●	●	●	●	⊗	●	○											
Penicillin Allergy De-labeling Pilot	Can we safely de-label patients with risk stratification and test dose amoxicillin challenges in patients who are at low risk of having an ongoing penicillin allergy?	VUH	Prognostic Model + BPA		●	●	●	N/A	●	●	●	●	●	●	●	●	●	AJRCCM	⊗	⊗	⊗	●	⊗	⊗	⊗	⊗	●
Penicillin Allergy De-labeling Stepped Wedge Trial	Can we safely de-label patients with risk stratification and test dose amoxicillin challenges in patients who are at low risk of having an ongoing penicillin allergy?	VUH	Prognostic Model + BPA		●	●	●	CL	●	●	●	●	○	⊗													

Current Learning Healthcare System Pipeline



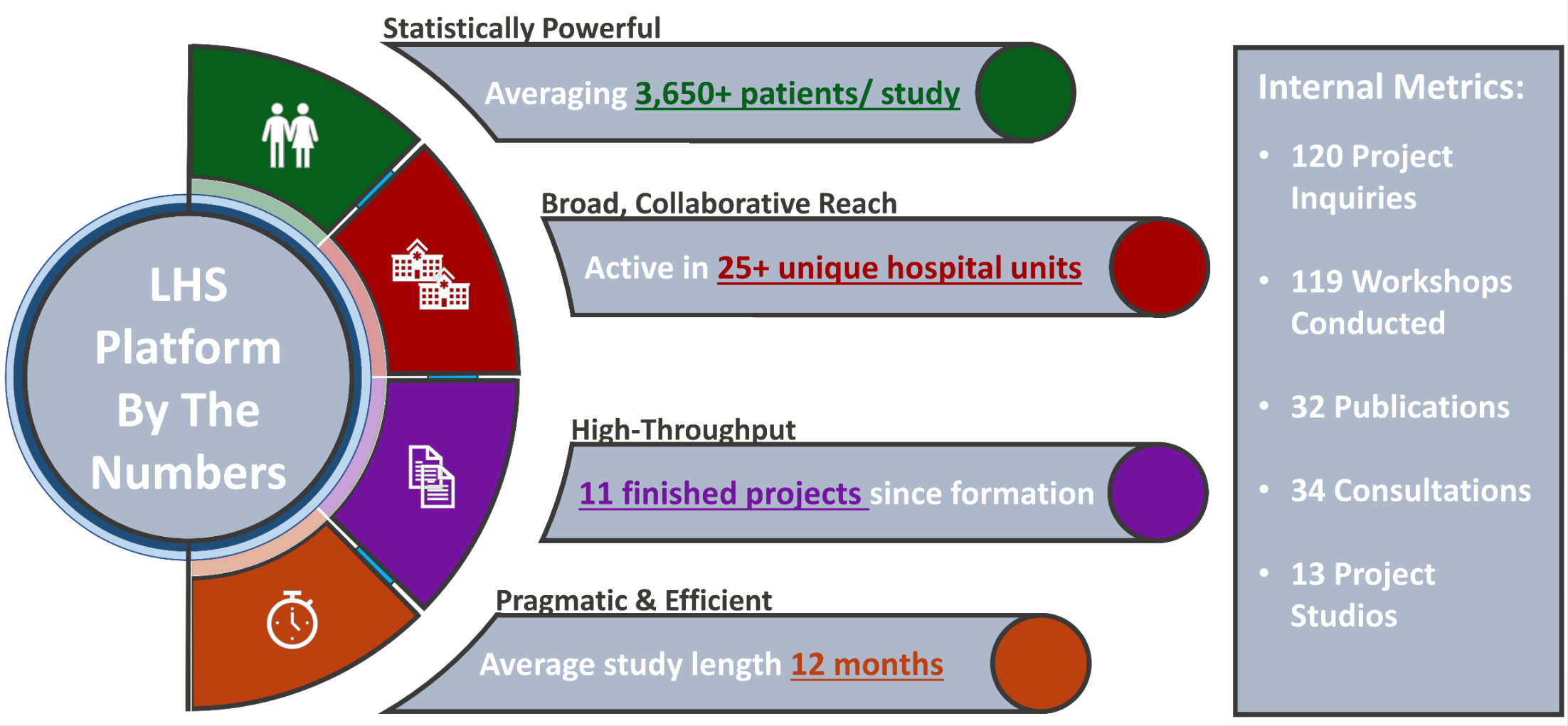
REVIEW/DESIGN KEY

Hospital · Ambulatory · A Adults · P Pediatrics

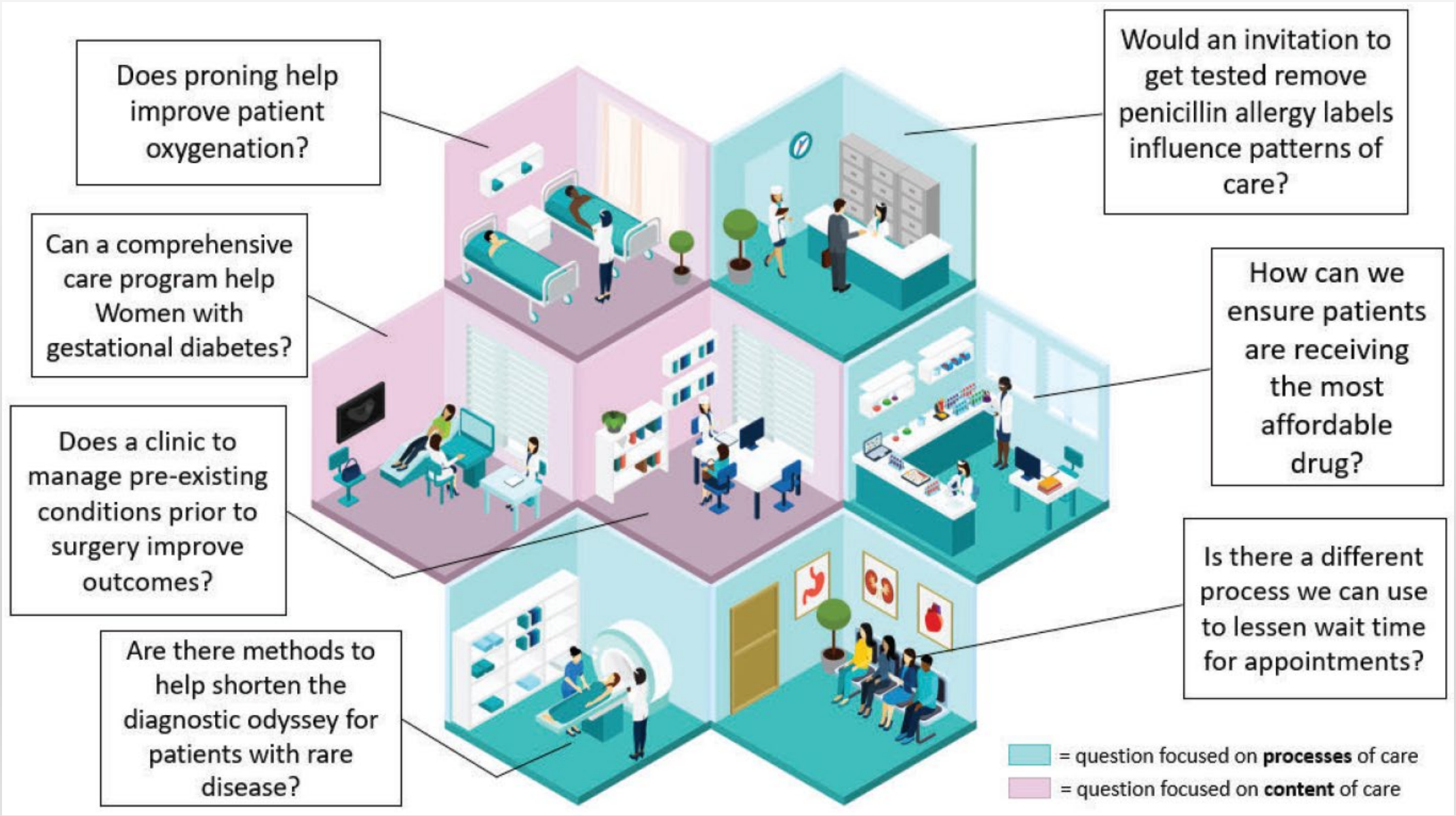
DISSEMINATION KEY

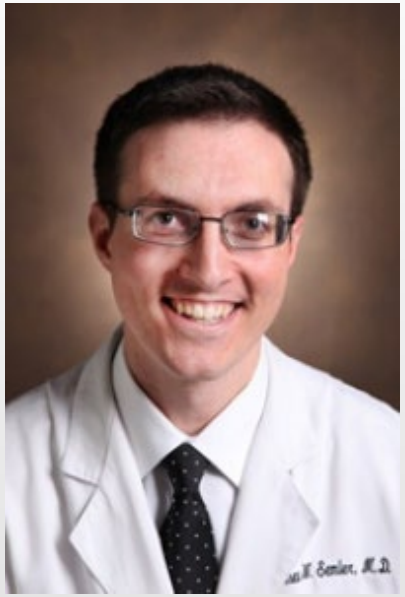
Conferences · Publication · Community Sharing · Clinical Practice

2021 Year End Project Overview



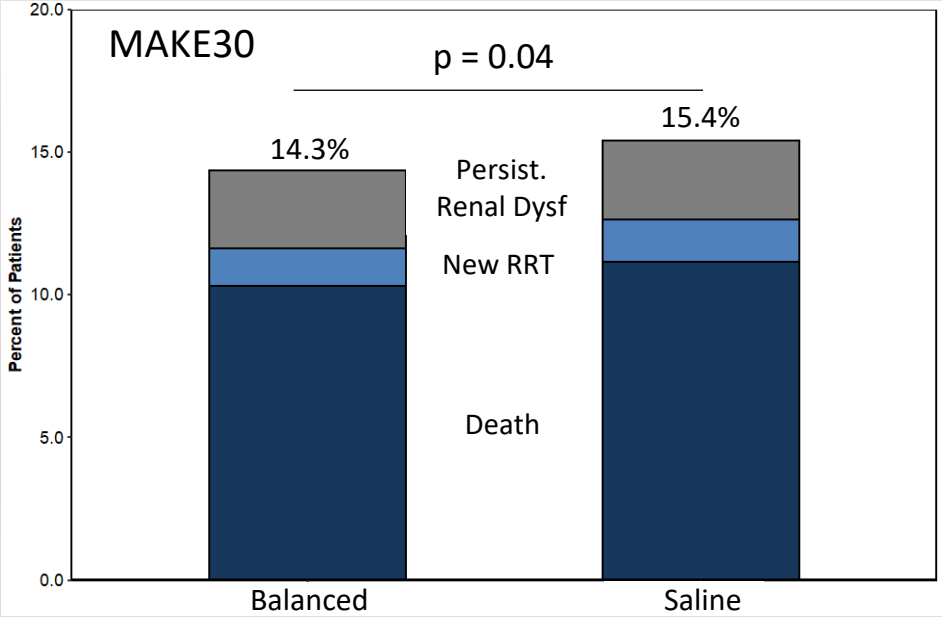
LHS Infrastructure Can Support Variety of Studies





Matt Semler, MD, MSCI
Department of Medicine
Division of Allergy, Pulmonary and Critical Care Medicine
Assistant Professor, K23 awardee (NHLBI)

- Pragmatic trialist involved in several LHS studies
- SMART - Isotonic Solutions and Major Adverse Renal Events Trial



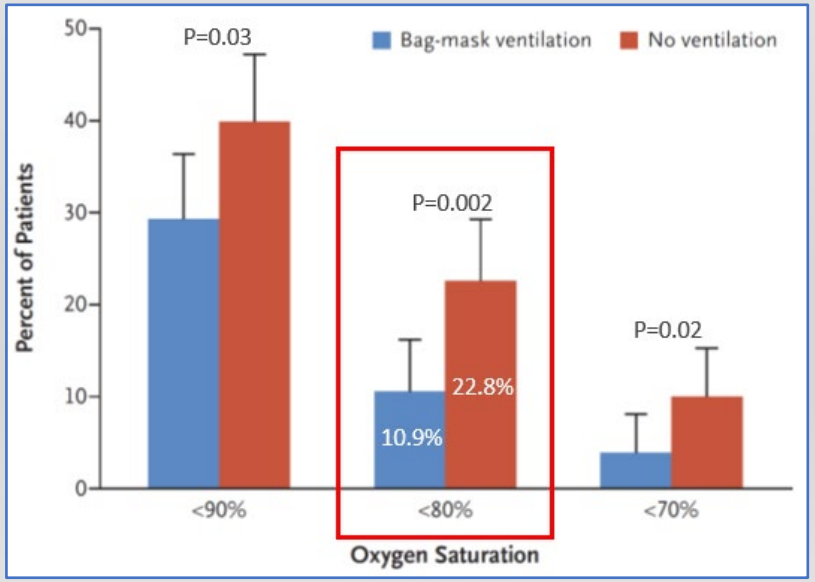
N = 15,802

- Compared the effect of saline vs. balanced crystalloids on the development of major adverse kidney events within 30 days (MAKE30) in patients admitted to the ICU
- Design: cluster RCT with multiple cross-over

N Engl J Med 2018;378:829-39.

Jon Casey, MD, MSCI
Department of Medicine
Division of Allergy, Pulmonary and Critical Care Medicine
Assistant Professor, K23 awardee (NHLBI)

- PreVent Trial: Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation
  - RCT of bag-mask ventilation before emergency intubation



- 7 ICUs in U.S.
- 401 patients randomized by sealed envelopes
- Intervention by treating clinicians, resp therapists
- Simple 1-page data collection sheet
- Bag-mask ventilation reduced hypoxia by half without increasing aspiration

Casey, Semler et al. *N Engl J Med.* 2019

Cosby Stone, MD, MPH
Department of Medicine
Division of Allergy, Pulmonary and Critical Care Medicine
K12 Learning Health System Scholar

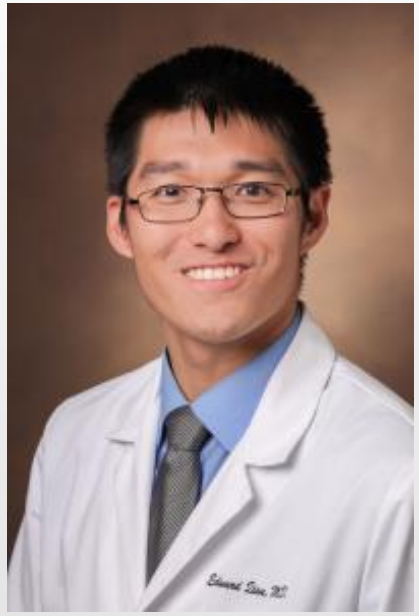
- First trial with LHS Platform: PROPEL
  - Examining the safety, effectiveness, and impact of a single dose oral amoxicillin challenge as a testing strategy to remove low-risk penicillin allergy labels
  - Stepped-wedge randomized controlled trial
  - Vanderbilt University Adult Hospital
  - Successfully removed over 200 penicillin allergy labels
- Develop a second LHS study: PALER
  - Vanderbilt clinics
  - Determine if providing an invitation to receive outpatient penicillin allergy testing increases uptake of testing and influences subsequent patterns of patient care

Autumn Zuckerman, PharmD, BCPS, AAHIVP, CSP
Program Director, VUMC Specialty Pharmacy

- Originally approached the LHS Platform to investigate outcome difference in patients with multiple sclerosis who receive care from the Specialty Pharmacy versus usual care
    - Attended the LHS workshop and redesigned

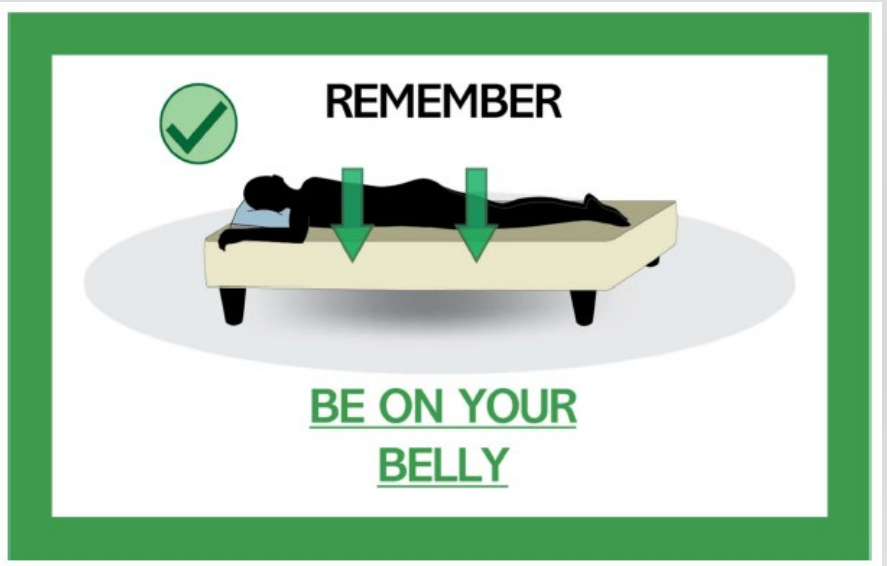
- Interventions to Improve Adherence in Vanderbilt Specialty Pharmacy
    - Examining whether a collection of interventions aimed at addressing nonadherence to therapy throughout 26 specialty clinics improves adherence rates

- Member of steering committee and other study teams evaluating pharmacy clinical services



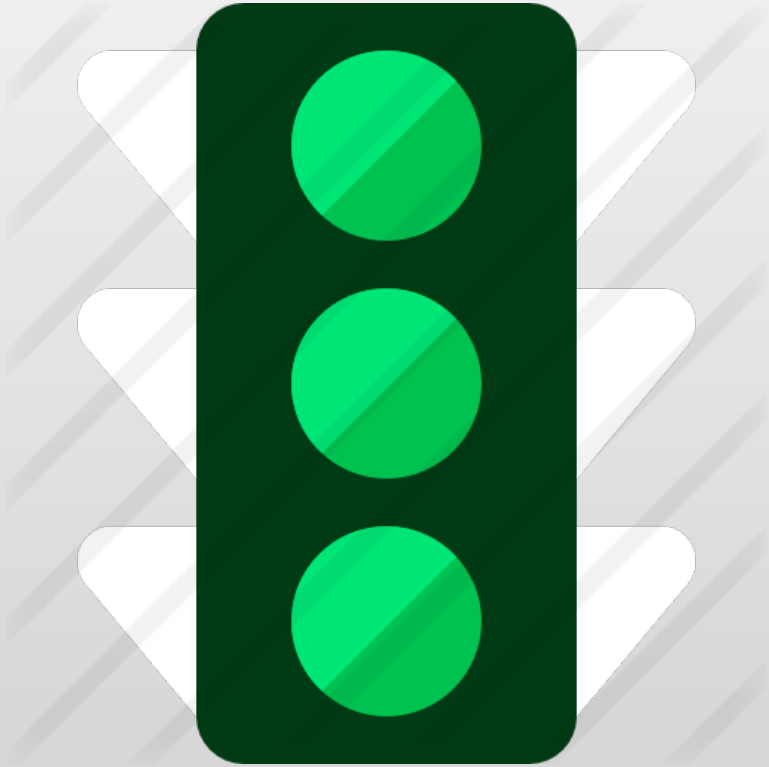
Edward Qian, MD
Department of Medicine
Division of Allergy, Pulmonary and Critical Care Medicine
Fellow

- Co-PI of an LHS Platform study launched in COVID-19 medical units
- Investigating the impact of recommending prone positioning while awake to patients hospitalized with COVID-19
    - Non-mechanically ventilated
- Quasi-randomized controlled trial
    - Study assignment by medical record number (odd/even)



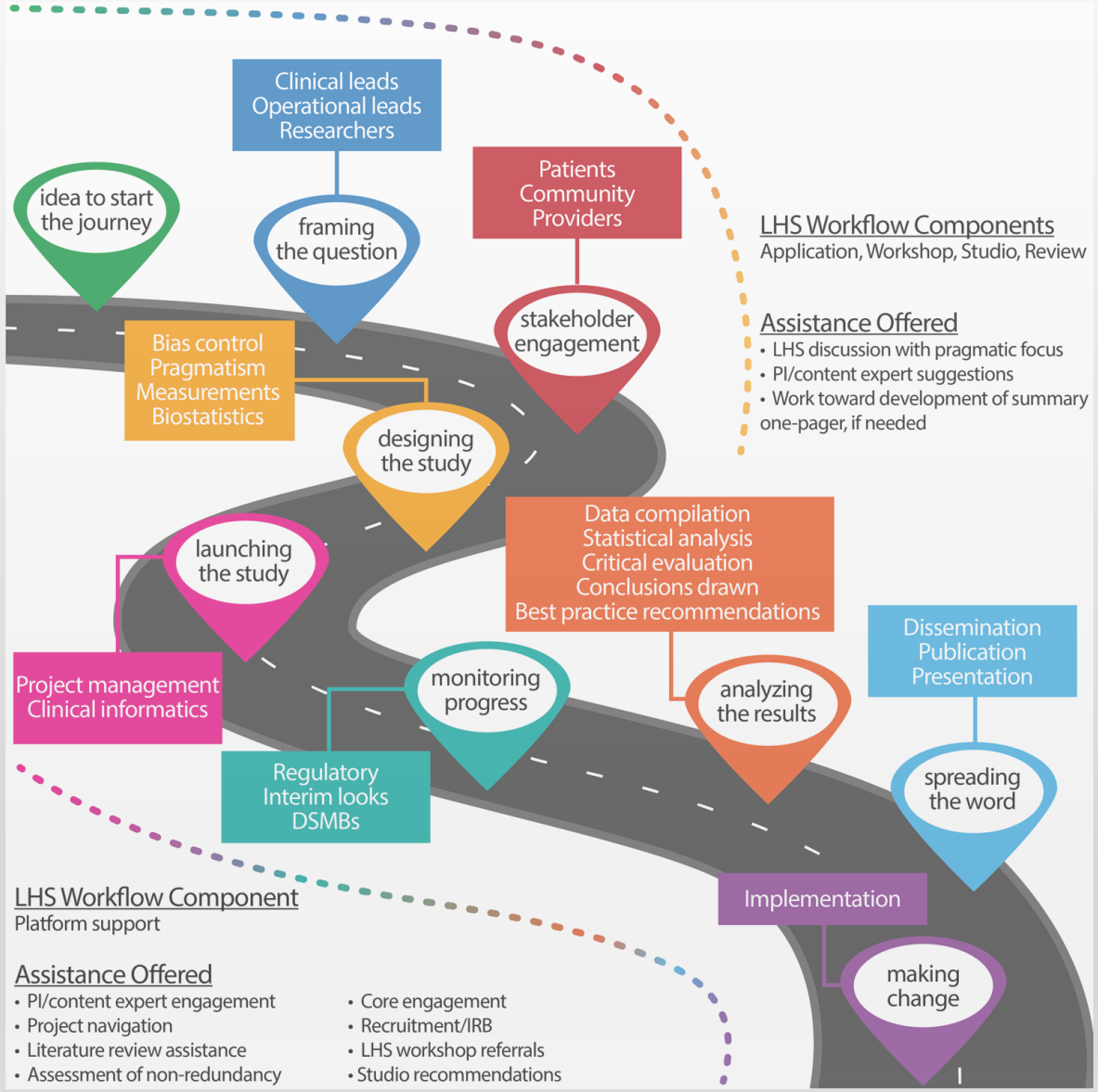
Learning Healthcare Facilitators

- Seek commitment at the highest levels early in the process: buy-in is CRITICAL
- Develop leadership and system change strategy
- Define clear and agreed upon interventions
- Define resource requirements
- Establish performance measures and set goals
- Ensure monitoring is feasible and pragmatic
- Collaborate and facilitate
- Drive with evidence-based recommendations



Learning Healthcare Barriers

- Lack of resources to support the effort – from research, operations, and learning perspectives
- Educating around the initiative without changing structures or expectations
- Tackling too much at once
- Measuring nothing or everything
- Failing to build support for replication
- Assuming that the status quo is OK
- Resistance to change or skepticism
- Lack of cooperation
- Burdensome data collection
- Lack of equipoise – unwillingness to randomize



Evolution of LHS

- Advancements
- How “pragmatic” is it?
- How to specify interventions for replicability?
- What about complex healthcare interventions?

Current/Future Directions

- Implementation science
- Additional areas

Regulatory and Methods Advancements

Regulatory

- Embedded consent – IMPACT-ERAS
- DSMBs – IMPACT-ERAS, ACORN

Methods

- Multi-site Engagement – PreVent
- Pilot to Hospital-wide Stepped Wedge – PROPEL
- Bayesian Analytic Approach – COVID Proning
- Formalizing Data Pathways – RD, VAPIR, VCLIC, Epic Physician Builders

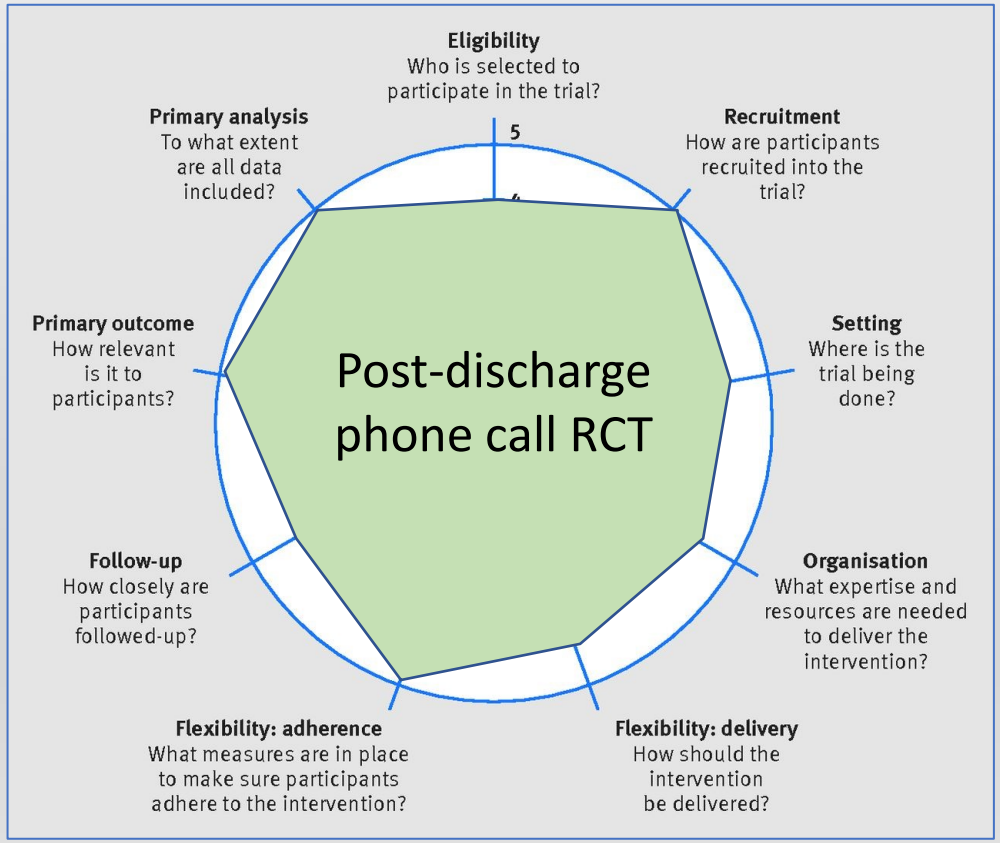
Visibility

- Team Expansion
- Twitter Presence
- Creative Forms of Dissemination

How "Pragmatic" Is It?

PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2)

- 9 domains, rate pragmatic (5) to explanatory (1)



Practically, we focus on 4 areas:

1. Is it feasible to randomize at the patient, provider, unit, or system level?
2. Will the approach require detailed, individual level informed consent?
3. Are relevant, reliable, and valid data readily available for
   a. identifying patients of interest, and
   b. evaluating outcomes?
4. Is patient volume sufficient for a study to have the power to draw meaningful conclusions within a reasonable timeframe, typically a year or less?

Loudon et al. *BMJ* 2015;350:h2147
https://www.precis-2.org/

Yiadom et al. *BMJ Open* 2018
Yiadom et al. *Med Care* 2020

Template for Intervention Description and Replication (TIDieR)

- Useful schema for specifying details of intervention
- Extension of CONSORT (2010) and SPIRIT (2013) guidance for reporting trials
- 12-item checklist

1) Brief name	7) Where
2) Why – rationale, theory	8) When, how much
3) What – materials	9) Tailoring – if adapted, how
4) What – procedures	10) Modifications
5) Who provides, expertise, training	11) How well – fidelity plans
6) How – modes of delivery	12) How well – actual fidelity

Hoffmann et al, *BMJ* 2014

Complex Interventions

Complexity

- Multiple interacting components, multiple causal pathways
- Intervention adaptable, flexible, multi-level
- Real world: contextual factors at play, health care staff carry out intervention

Challenges in studying

- Heterogeneity: patients, microsystems, context, intervention
- Variability/adaptability: intervention targets, context, intervention content
- Causal complexity: multiple components, multi-step causal chains, strength of contextual vs main effects
- Contextual factors affect implementation strategies, processes, and outcomes

Craig et al, *BMJ* 2008;337:a1655
Guise et al, *J Clin Epidemiol* 2017

PCORI Standards for Studies of Complex Interventions

SCI-1: Fully describe the intervention and comparator and define their core functions.

- Functions, forms, intervention target

SCI-2: Specify the hypothesized causal pathways and their theoretical basis.

- Include contextual factors that may influence impact

SCI-3: Specify how adaptations to the form of the intervention and comparator will be allowed and recorded.

- What is allowable, how managed and measured, maintain fidelity to core functions

SCI-4: Plan and describe a process evaluation.

- Fidelity, dose actually delivered, reach, mediators, moderators

SCI-5: Select patient outcomes informed by the causal pathway.

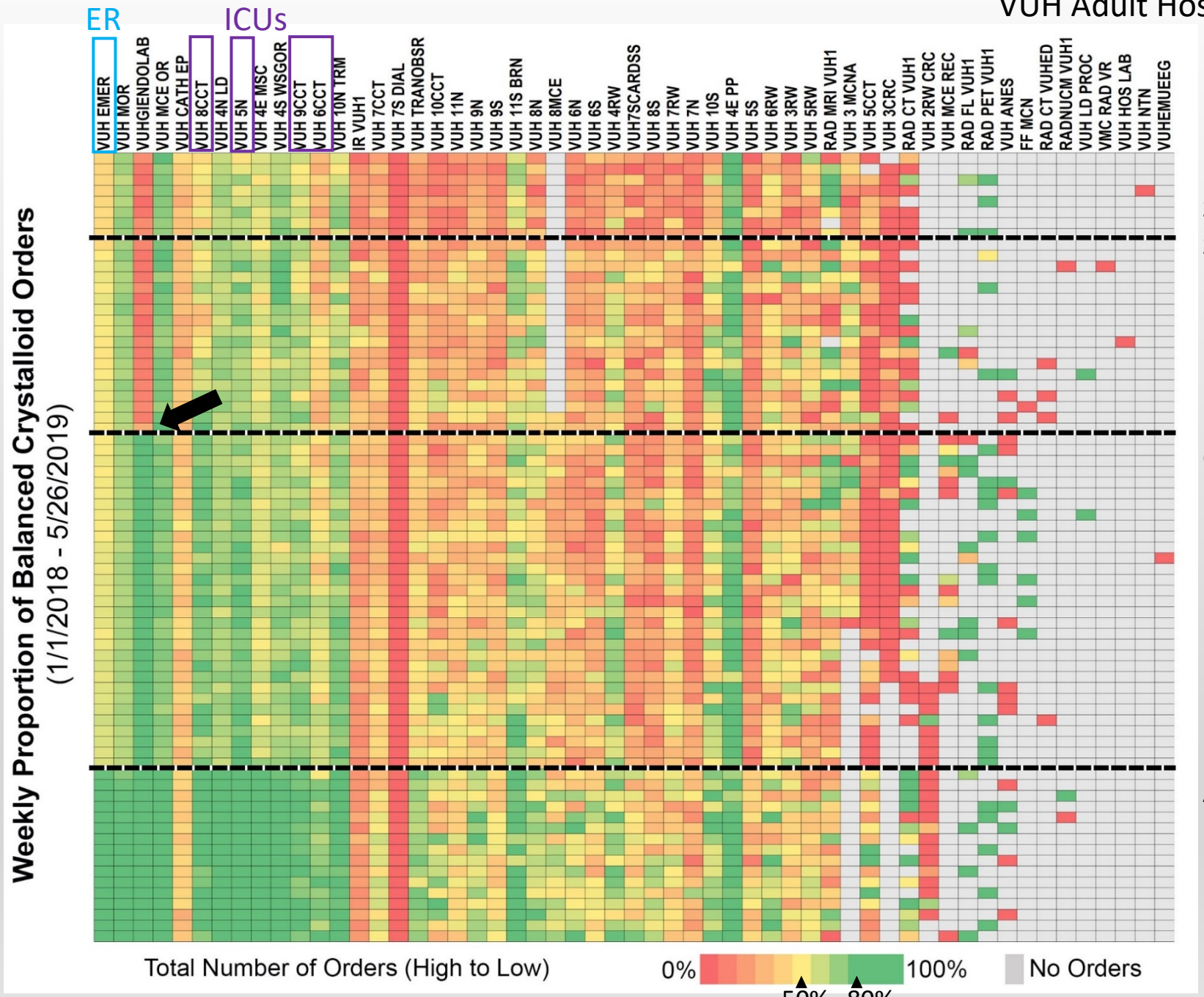
https://www.pcori.org/research-results/about-our-research/research-methodology/pcori-methodology-standards#Complex

Current and Future Directions

Further Incorporation of Implementation Science

- Hybrid effectiveness-implementation trials
  - Type 1: Primary focus on effectiveness, also evaluate implementation
  - Types 2 and 3: Test implementation strategies
- Intervention fidelity: run-in period and monitoring
  - Example: COVID-19 proning study
- Dissemination
  - Toolkit of resources for dissemination
  - QuizTime asynchronous learning platform
- After trial completion: disseminate, implement, sustain
  - Example: SMART, SALT-ED studies
  - Dashboard monitoring of practice, clinical decision support tools

VUH Adult Hospital



SMART/
SALT-ED
Published

Modified Orderable
GI-ENDO Lab

Modified Orderable
Admissions

Dear, Buie, Lindsell

Current and Future Directions

Additional Areas for Expansion

- Scaling to ambulatory and pediatric settings
- Incorporating health equity
- Data science, predictive analytics
- Bayesian analysis
- “Precision LHS”
  - Heterogeneity of treatment effects, estimate effects for individual patients
- Network resources, online tools
  - Epic to REDCap modules, MyCap for patient data collection, randomization modules, workshop facilitation materials

Thank you!

Questions?

Contact us:
sunil.kripalani@vumc.org
learninghealth@vumc.org

@Kripalani_Sunil
@VUMCLHS