Ethical and Regulatory Challenges/ Lessons Learned

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NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Panelists

- Michele Balas, PhD
  - Behavioral Economic and Staffing Strategies to Increase Adoption of the ABCDEF Bundle in the ICU (BEST-ICU)
- Diana Burgess, PhD
  - Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP)
- Richard Skolasky, ScD
  - Advancing Rural Back Pain Outcomes through Rehabilitation Telehealth (ARBOR-Telehealth)

Session Goals

- Hear from the NIH Collaboratory Trials about ethical and regulatory challenges encountered
- Discuss strategies for navigating ethical and regulatory complexities of ePCTs

BEST ICU Trial: Ethical & Regulatory Issues Lessons Learned

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Nebraska Medicine

Disclosures

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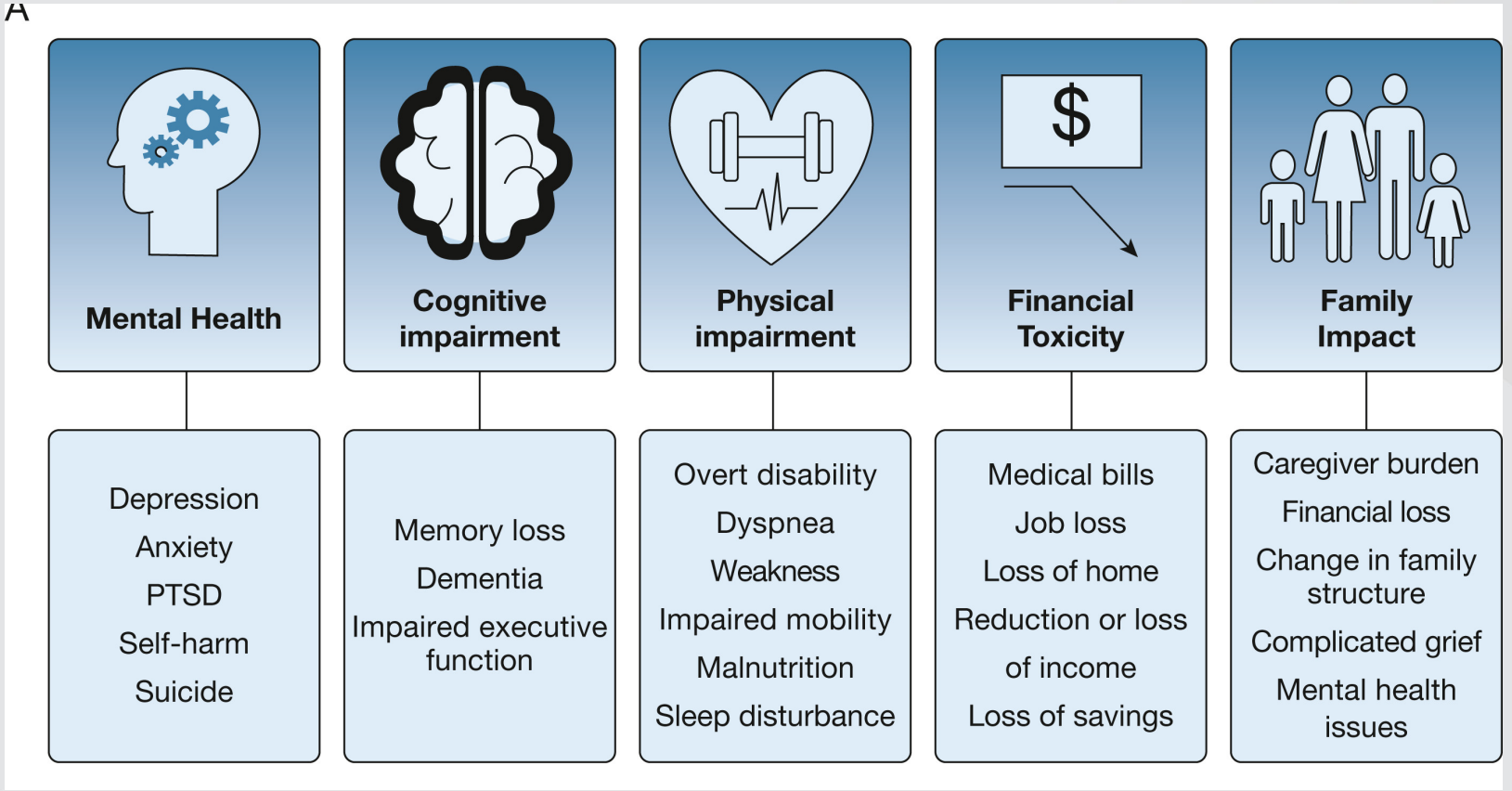
- Serves as Co-chair for:
  - SCCM's PADIS Guideline Committee
  - AACN's Healthy Work Environment Collaborative
- Past honoraria from:
  - SCCM
  - AACN
  - Ceribell

Problem Addressed: Human & Financial Costs of ICU Survivorship



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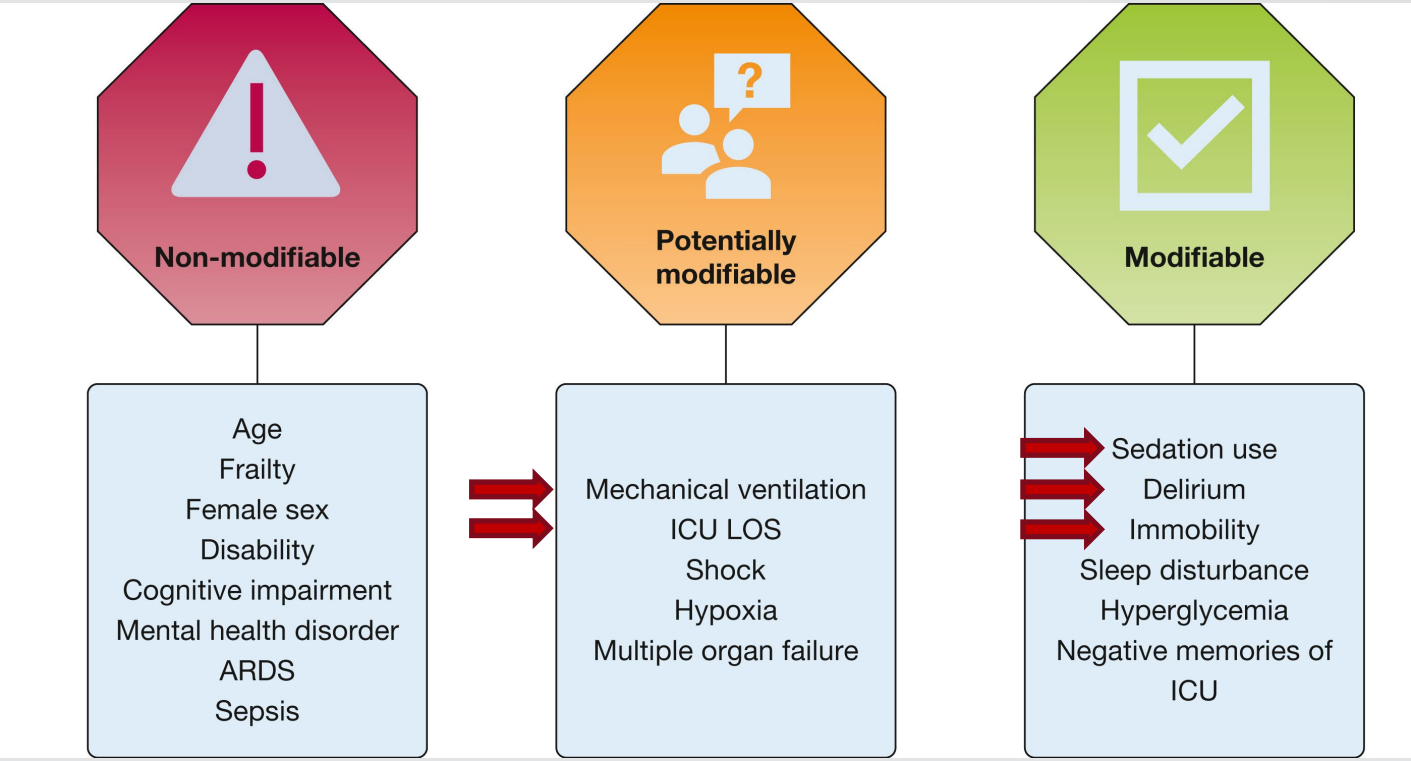
Risk Factors for Problem



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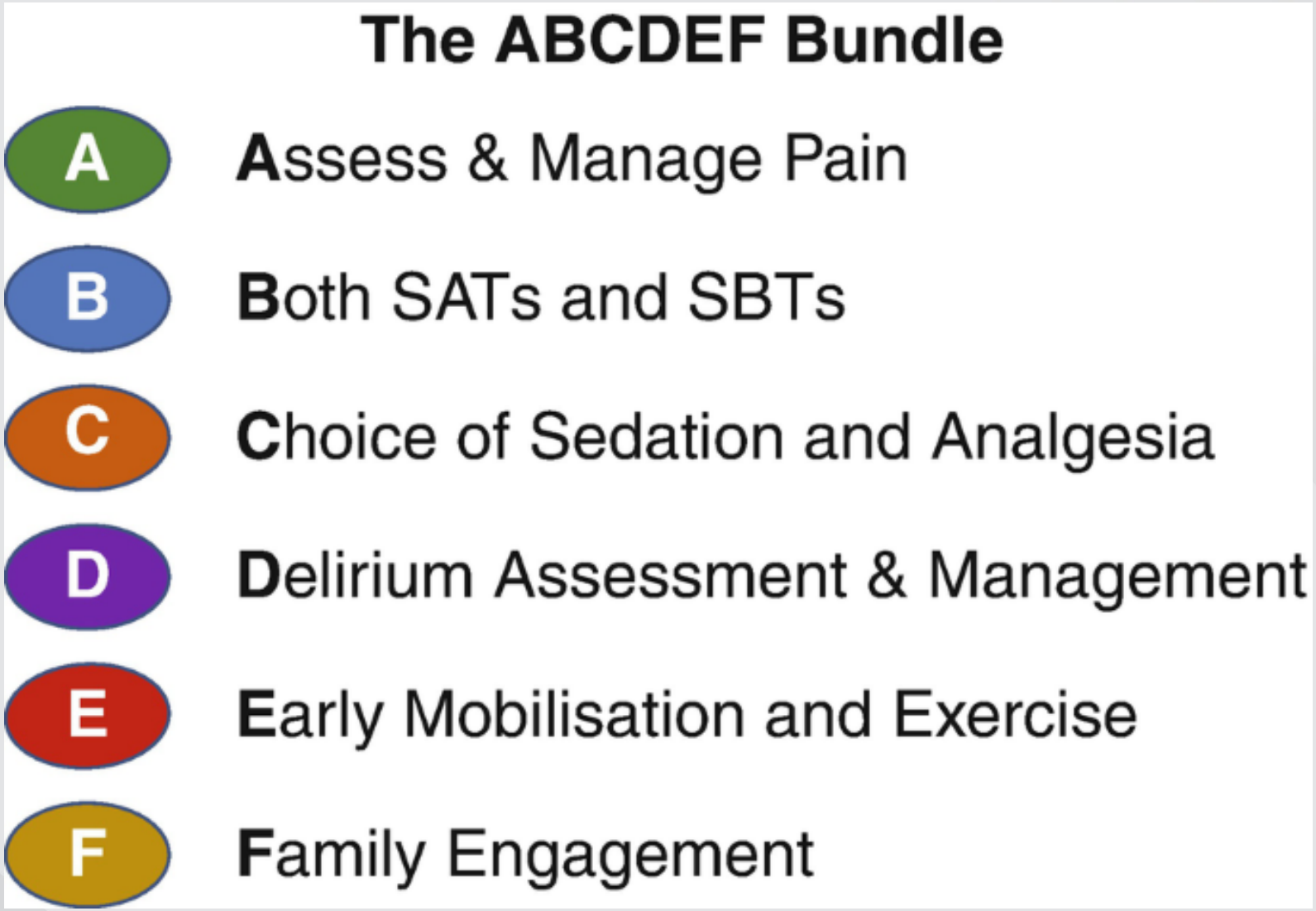
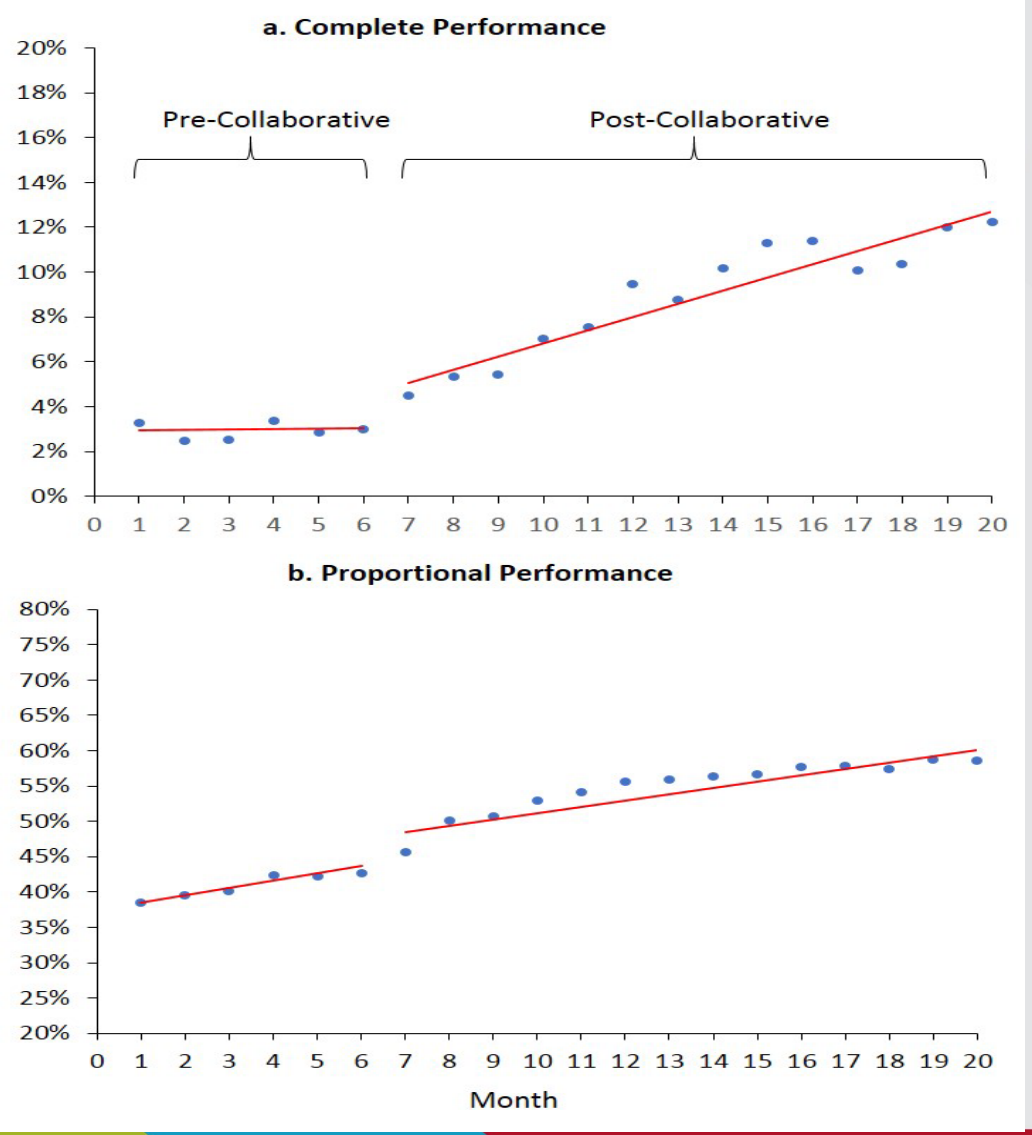
Solution to Problem



Implementation Gap



Trial Goals, Objective, & Design

- **B**ehavioral **E**conomic & **St**affing Strategies to Increase Adoption of the ABCDEF Bundle in the ICU (BEST-ICU)
  - Overarching Goal: Support the “real-world” assessment of strategies used to foster adoption of several evidence-based clinical practices in healthcare systems that provide care to critically ill adults with known health disparities
  - Objective: Evaluate two discrete strategies grounded in behavioral economic & implementation science theory to increase adoption of the ABCDEF bundle
  - Design: 3-arm, pragmatic, stepped-wedge, cluster randomized hybrid type III effectiveness-implementation trial

UH3 Aims

- **Aim 1:** Compare the effectiveness of real-time audit & feedback & RN implementation facilitator on ABCDEF bundle adoption (**primary study outcome**)
- **Aim 2:** Compare the effectiveness of real-time audit & feedback & RN implementation facilitator on clinical outcomes (duration of MV; ICU, hospital, & 30-day mortality; ICU & hospital length of stay; days with acute brain dysfunction; discharge disposition, psychoactive medication, discharge physical therapy utilization; & 30-day hospital readmission)
- **Aim 3:** Identify & describe key stakeholders' experiences with, & perspectives on, the acceptability & impact on work intensity of real-time audit & feedback & RN implementation facilitator

UG3 Ethical & Regulatory Challenges

- Data & Safety Monitoring Plan Development
  - Risk/benefit of what?
    - Implementation interventions, evidence-based practice interventions (previously established safety & efficacy), both?
      - Consideration of harms of not getting evidence-based interventions
  - Complexity of monitoring adverse events & blinding in pragmatic clinical trials
    - EHR data lag, challenges of deidentified data
    - Site PI contact with intervention & staff
    - Website for reporting

UG3 Ethical & Regulatory Challenges

Events that will be tracked as clinical outcomes & will not therefore be reported as AEs during the study (unless believed to be study related and/or more severe or prolonged than expected given the nature of the underlying illness).

- Hospital mortality
- Duration of mechanical ventilation, stratified by survival status
- Clinically significant falls acquired during hospitalization
- Tachyarrhythmias requiring treatment
- Cardiac arrest
- Reintubation within 24 hours of extubation

UG3 Ethical & Regulatory Challenges

- Data breach of confidential, patient-level PHI
- Audit & feedback dashboard error resulting in a clinical action that was not indicated & resulted in patient harm
- RN implementation facilitator action that was not indicated & resulted in patient harm
- ICU providers feelings of being unduly pressured or coerced by either implementation strategy (i.e., real-time audit & feedback dashboard, RN implementation facilitator)
- Other
- SUSARs
- Unanticipated Problems

UG3 Ethical & Regulatory Challenges

- DSMB reporting tables
  - How much & what kind of data required
- Current NIH templates
  - Geared toward traditional clinical trials, not dissemination & implementation science or pragmatic clinical trials
    - Would be valuable to have various templates
- Different NIH reporting forms (protocol, DSMB charter, DSMP)
  - Called out on redundancy, however NIH reporting templates have this redundancy built in

Reaching Rural Veterans: Applying Mind-Body Skills for Pain Using a Whole Health Telehealth Intervention (RAMP)

Diana J. Burgess, PhD

Core Investigator, Center for Care Delivery and Outcomes Research, Minneapolis VAHCS

Professor, University of Minnesota Medical School

Director, VA QUERI Complementary and Integrative Health Evaluation Center (CIHEC)

RAMP

Rural Veterans Applying Mind Body Skills for Pain

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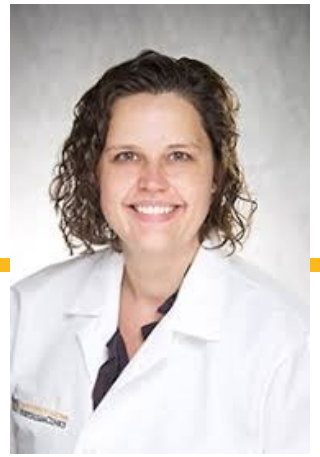
RAMP

Acknowledgements



Co-PIs: Katie Hadlandsmyth, PhD and Roni Evans, DC, PhD

Research Team: Co-Investigators: Robin Austin, John Ferguson, Alex Haley, Brent Leininger, Marianne Matthias, Brent Taylor, Stephanie Taylor; Consultant: Greg Serpa

Project staff: Ann Bangerter, Lee Cross, Emily Hagel Campbell, Mallory Mahaffey

RAMP Study Overview

Phase 1 UG3 (2 years): Engagement activities including developing & working with multi-level advisory panels (n = 35-50) & single arm pilot study (n = 40)

Phase 2 UH3 (3 years): Hybrid Type II Effectiveness Implementation Pragmatic Clinical Trial

1. Assess **effectiveness** of cohesive mind-body intervention delivered by Whole Health coaches via telehealth (RAMP), at improving pain and secondary outcomes among rural VA patients with chronic pain (n = 500)

2. **Implementation**. Work iteratively with multiple levels of advisors (patients, community advisors, VA healthcare system leaders and staff; n = 35-50) to co-develop, evaluate intervention implementation strategies used in the trial and adapt these strategies to scale up RAMP within the national VA healthcare system
   a. **Mixed-methods assessment** of facilitators/barriers, RAMP use, etc.
   b. **Co-creation** of plausible implementation strategies to scale up RAMP
   c. **Budget impact analysis**

RAMP

Accountable to many entities; don't always align; distinguishing between "have to" and "suggestions"

NIH Project Scientist and Program Director

HEAL (e.g., data collection and repository requirements)

NIH Pragmatic trials Collaboratory Workgroups (Ethics & Regulatory, Biostatistics)

Data Safety Monitoring Board

- **Institutional Review Boards**
  - **Minneapolis VA IRB and VA R&D (primary)**
  - **University of Iowa IRB**
  - **University of Minnesota IRB**

Example: NIH and Mpls IRB have different protocol templates and requirements in terms of level of detail

Solution: Regular communication, especially with project scientist, program director and our local IRB

RAMP

Ambiguity over role of Veteran, Community, and Internal (VA) Advisors

- Advisors are explicitly not considered research participants, although we plan to use their data; different interpretations by IRBs
  - Also, employees are considered vulnerable
- Solution:
  - Worked closely with Minneapolis IRB to create a tailored approach; advisors considered participants for regulatory purposes
  - Explained to the Iowa IRB what was established in Minneapolis IRB so both align
  - Explain issue to advisors

RAMP

Ethical & pragmatic approaches designed to maximize external validity can be at odds with more traditional beliefs about rigor (RCTs, maximize internal validity)

- **Example:** We are not denying participants the use of additional pain treatments during trial of mind-body approaches to pain; concern that this could water down effects
- **Solution**: Work closely with project scientist to address concerns (in this case, carefully measure other treatments used)
- **Broader solution:** Promote the values of pragmatic trials; can be tradeoffs pragmatic and explanatory elements

RAMP

Advancing Rural Back Pain Outcomes through Rehabilitation Telehealth (ARBOR-Telehealth)

MPIs: Richard L. Skolasky, ScD; Kevin McLaughlin, DPT

Funded by National Institute of Arthritis and Musculoskeletal and Skin Diseases (UG3AR083838)

Overview

Low Back Pain (LBP)

- Most common cause of disability in the US
- Largest driver of US healthcare spending growth
- Number one reason for opioid prescriptions

Physical Therapy (PT)

- First line treatment
- Cost-effective in reducing disability and pain
- Decreased risk of opioid use
- 7-13% of patients attend PT
  - Barriers surrounding travel, missed work time, etc.

Overview

Rural Communities

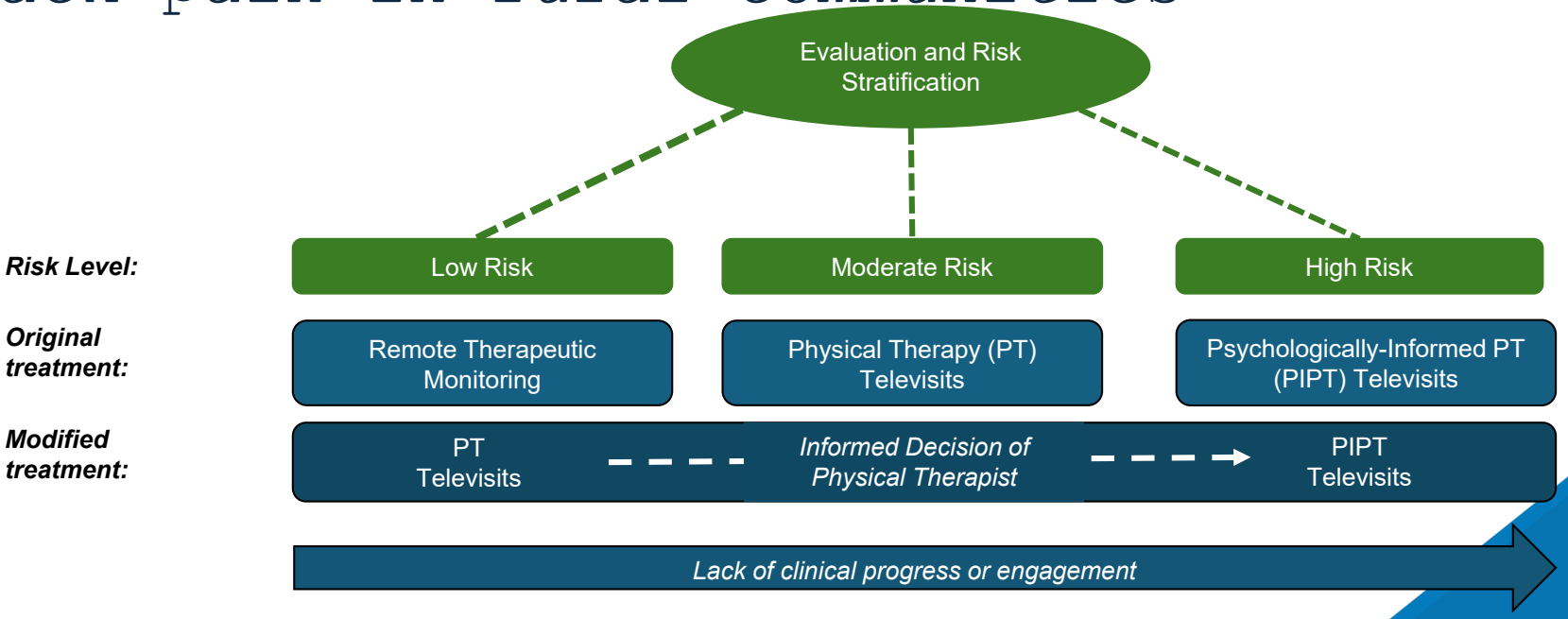
- 40% fewer therapists per capita
  - Longer distance to travel
- Fewer patients attend PT within 30 days of onset
- Higher rates of opioid use

Telehealth

- PT provided by televisits for first time during pandemic
- Reimbursed by CMS and most commercial insurances
- New code for remote therapeutic monitoring (RTM)
  - Asynchronous telerehabilitation using

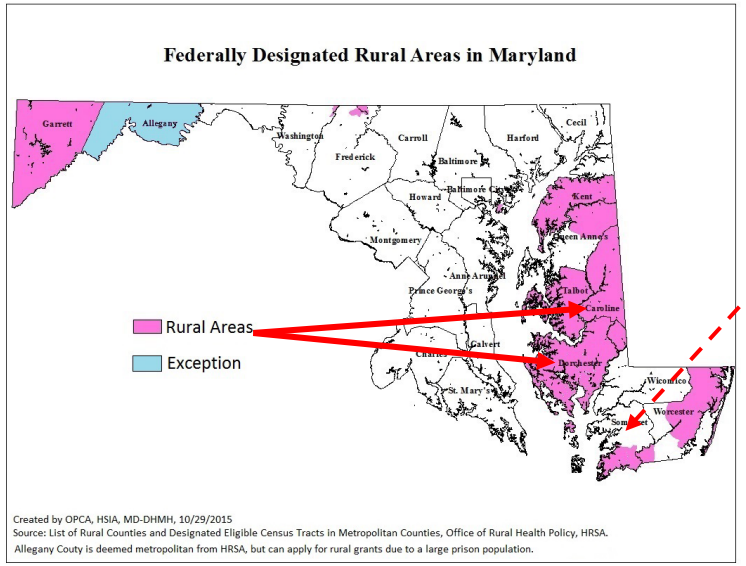
Overall Objective

- To compare the effectiveness of a risk-informed telerehabilitation model to patient education to improve outcomes in patients with chronic low back pain in rural communities



Study Design

- Randomized clinical trial
  - RiSC Telerehabilitation
    - Delivered by TidalHealth
  - Patient Education
    - Delivered via website
- Patients
  - 434 with chronic LBP
    - No spine surgery past 12m
    - Primary care office visit
  - 8 weeks active treatment
  - 12 months follow-up



Nearest PT Clinic

Caroline County, MD
- *33,593 (pop'n est. 2023 Census)*
- *80.7% White, 13.8% Black, 8.9% Hispanic*
- *17.7% Age 65+ years*

Dorchester County, MD
- *32,897 (pop'n est. 2023 Census)*
- *66.4% White, 29.2% Black, 6.4% Hispanic*
- *23.1% Age 65+ years*

Potential Facilitators

Treatment Strategy

- Clinical experience
  - JH implementation of telehealth strategies
- Research experience
  - Seasoned team of JH researchers
  - Tidalhealth Richard A. Henson Research Institute

Institutional Review Board

- JH Clinical Research Network
  - Network of independent hospitals
  - History of collaboration on ethical and contractual issues
- JH IRB
  - Experience with reliance

Potential Facilitators

HIPAA Privacy Waiver

- EHR-based recruitment
  - IRB-approved plan to create Model Recruitment dataset
  - *IRB-review plan to generate monthly list of potentially eligible patients*

Informed Consent

- EHR integration
  - Intervention adherence
  - Fidelity assessment
  - Healthcare use
- REDCap platform
  - Patient-reported outcomes
- Secondary data
  - Area Deprivation Index (ADI)
  - *Others*

Potential Barriers

Treatment Strategy

- Risk-based care model
  - How to discuss 'risk' with participant
  - Concern for *knock-on* effect
    - Patient discusses high-risk status with provider
    - Patient adopts a high-risk persona

Study Risk Level

- Minimal vs. More-than-Minimal

Potential Barriers

Institutional Review Board

- Johns Hopkins
  - Review Board of Record
- Tidalhealth
  - Research Review Committee
  - WCG

Data Safety Monitoring Plan

- NIAMS appointed
  - Study team input
- Program officer
  - Protocol changes

Study Team

- Johns Hopkins
  - Richard L. Skolasky, Sc.D. (MPI)
  - Kevin McLaughlin, D.P.T. (MPI)
  - Elizabeth Colantuoni, Ph.D.
  - Stephen Wegener, Ph.D.
  - Tricia Kirkhart
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- TidalHealth
  - Robert Joyner, Ph.D.
  - Jill Stone, D.P.T.
  - M. Patricia Chance, CRRC
  - Terri Hochmuth, D.N.P., M.S.N.-Ed, R.N.
- Maryland Rural Health Association
  - Jonathan Dayton, Director

Questions