

# Clinical Considerations & Operational Challenges for Healthcare-Associated Infection (HAI) Prevention Trials

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# HAI Prevention Trials

- ***Common features***
  - Desire to evaluate a quality improvement (QI) strategy
  - Grouped focus: units, hospitals
  - Targeting a contagious outcome
  - Spurred by urgent, common need
  - Limited funds

# Common Features of Classical vs Pragmatic Trials

- ***Classical RCTs***

- Individuals
- Efficacy
- Wide risk range
- Placebo-controlled
- Informed consent

- ***Pragmatic RCTs***

- Populations
- Effectiveness
- Minimal risk
- Contemporaneous controls
- Waived consent

<sup>1</sup> Ford I & Norrie J NEJM 2016;375:454-63

<sup>2</sup> Ramsberg J & Platt R. Learn Health Sys 2018;2:e10044

<sup>3</sup> NIH Pragmatic Trials Collaboratory, <https://rethinkingclinicaltrials.org/>

# Efficacy vs Effectiveness Trials

- ***Efficacy***

- Seeks ideal conditions
- Highly selected patients
- Intensive recruitment
- Efforts for high compliance
- Trial infrastructure
- Compensation

- ***Effectiveness***

- Typical conditions
- Less selection the better
- Efficient recruitment
- Efforts for usual compliance
- Operational infrastructure
- Learning while doing

# Infection Prevention Populations

- ***Targets***
  - Units or clinics
  - Facilities (hospitals, nursing homes)
  - Special populations
    - Procedures (e.g., surgery, devices, lines)
    - Chronic illness (e.g., dialysis, diabetes)
    - MDRO carriers
    - Post-discharge

# Universal vs Targeted Populations

- ***Pragmatic Considerations***

- **Grouped interventions**

- Whole units, facility easier to train, implement
    - Outcomes often already tracked

- **Targeted populations**

- Requires flag or detection algorithm
    - Outcomes require special report tracking or detailed chart review
    - Individual outcomes (carriage) may require sampling

# Decolonization Population Targets

- **Examples**
  - **ICU decolonization**
    - Recruit and randomize ICUs (cluster-randomized)
    - Intervention ICUs receive order sets and protocols for new practice
    - Usual unit surveillance for outcomes: HO-MDRO, BSI, MRSA BSI
  - **Decolonization of MRSA carriers**
    - Use EHR MRSA flag
    - Recruit, consent, and randomize individuals
    - Individual outcomes require follow up for infection, clearance

# Selection of Question Under Study

- ***Temporary Prevention During High-Risk Period***
  - Focused intervention period
  - Limited follow up
  - Usual surveillance outcomes may suffice
- ***Long-lasting Prevention (e.g., MDRO clearance)***
  - Focused or lengthy intervention period
  - Longer follow up
  - Post-discharge or post-clinic outcomes needed
  - Trial-based laboratory surveillance

# Health System Partnership

- ***Design & Recruitment***
  - Academic-operational alignment, leadership partnership
  - System-based recruitment by system leadership
  - Clinics or hospitals within system
  - Patients recruited by system leaders
- ***Implementation***
  - System required IT solutions - order sets, adherence tracking reports, outcomes
  - System leadership agreement to avoid competing interventions

# Minimal Risk Trials and Waiver of Consent

- ***IRB considerations***
  - OHRP guidance: minimal risk and waiver of informed consent
  - FDA guidance (July 2017): allows for minimal risk waiver of consent <sup>1</sup>
- ***Who governs choice? Randomization Itself Does Not Require Consent***
  - Could hospitals implement the intervention currently under QI?
  - Do patients currently choose selected products?
  - Examples: hospitals select their drug formulary, device types, skin, soap and cleaning products

<sup>1</sup> <https://www.fda.gov/media/106587/download>

# Controls

- ***Contemporaneous***
  - Grouped randomization requires sufficient number
  - Accounts for secular trends
- ***Prior Baseline***
  - Allows control to self (individual or groups)
  - Accounts for unmeasured confounding
- ***Both***
  - Ideal set of controls
  - Enables difference-in-differences analytic approach



# Confounders

- ***Baseline Randomization***
  - Size of cluster-randomized trials often insufficient to assure balance
  - Specialized approaches: e.g., Goldilocks, can improve balance by accounting for multiple baseline values and assigning weights to them
- ***Analysis***
  - Comparison to own baseline then compared across arms (difference-in-differences approach)
  - Secondary analyses can be as-treated and/or adjusted

<sup>1</sup> Sturdevant SG et al. *Contemp Clin Trials Commun.* 2021;22:100746 (Goldilocks approach and app)

<sup>2</sup> Li F et al. *Stat Med.* 2016;35:1565-1579

# Competing Interventions

- ***At Baseline***
  - Different baseline activities
  - Solutions: large-scale randomization, difference-in-differences approach
- ***During Trial***
  - Continued interventions ok with difference-in-differences approach
  - New interventions require monitoring, dissuading, drop out
  - Example: REDUCE MRSA Trial: 69 ICU/hospital interventions proposed in 18-months, 36 conflicted with the trial and were not pursued

# Sample Size & Interim Analysis

- ***Special considerations***
  - Power and sample size remain essential
  - Likelihood of competing interventions favors larger, shorter trials
  - Same with likelihood of secular trends, guideline changes
  - Interim analysis for safety assessment often unnecessary with minimal risk trials and would prolong trial time

# Analysis: Critical Elements

- ***Special considerations***

- Outcomes contagious, non-independent → accounting for clustering important for group interventions to account for within group vs between group effects (person-level, unit or hospital level)
- Often need to simulate intra-cluster correlation to estimate power
- Difference-in-differences approach has advantages to address confounding, pre-existing competing interventions
- Statistician with expertise in non-independent events is important

# Tale of Two Trials

## CLEAR Trial

- Individual-randomized trial of 2121 discharged MRSA carriers comparing routine care vs repeated decolonization with 1 year post-discharge follow up
- Outcomes: time to 1<sup>st</sup> MRSA infection, any infection, and hospitalization

## REDUCE MRSA Trial

- Cluster-randomized trial of 74,256 ICU patients in 43 hospitals comparing 3 groups: routine care, targeted decolonization, and universal decolonization
- Outcomes: time to 1<sup>st</sup> ICU HO-MRSA culture, MRSA BSI, any BSI

<sup>1</sup> Huang SS et al. NEJM 2013;368(24):2255-2265.

<sup>2</sup> Huang SS et al. NEJM 2019;380(7):638-650.

# Tale of Two Trials

## CLEAR Trial

- Randomized Individuals
- 3y intensive recruitment
- Individual consent
- Compensation
- Extensive contact/visits
- Intensive chart reviews
- Outcomes: 2+ years
- \$10 million total trial
- \$4,673 per patient

## REDUCE MRSA Trial

- Randomized hospitals
- 8-week recruitment
- Waiver of informed consent
- No compensation
- Usual hospitalization
- Data from clinical warehouse
- Outcomes + Analysis: 9 mo
- \$3 million total trial
- \$40 per patient

<sup>1</sup> Huang SS et al. NEJM 2013;368(24):2255-2265.

<sup>2</sup> Huang SS et al. NEJM 2019;380(7):638-650.

# Cross Trial Comparisons

- ***Guideline Concerns for Infection Prevention***
  - Trials demonstrate effectiveness with one type of control group
    - Gold standard controls change with time
    - Effective interventions may be against an “old” control
    - If three interventions are effective against the same type of control group, does it mean all should be implemented?
  - Specifying controls in guidelines may be necessary and important

# Pragmatic Trials and FDA Indications

- ***Special considerations for minimal risk indications***
  - Gold standard for infection prevention often arises from studies and trials not undertaken by companies seeking indications
  - Pragmatic trials often are not structured to achieve FDA indications
  - Can/should those trials be used by companies to obtain indications
  - Lack of indication can hamper adoption due to lack of manufacturer guidelines or available training for that type of use

# Prevention Trial Summary

- ***Wide variety and duration of trials can be pursued***
- ***Ensure***
  - Consider value of group vs individual randomization
  - Sufficient sample size for balancing confounders, assessing outcomes
  - Controls performing best practice for gold standard comparison
  - Account for contagious outcomes in analysis
  - Ensure data for as-randomized analysis when groups drop out
  - Assess and disclose competing interventions