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

Susan Huang, MD MPH
Professor, Division of Infectious Diseases
Medical Director, Epidemiology & Infection Prevention
University of California, Irvine School of Medicine

UC Irvine Health
School of Medicine

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

[1] Ford I & Norrie J NEJM 2016:375:454-63
[2] Ramsberg J & Platt R. Learn Health Sys 2018;2:e10044
[3] 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 [1]
- ***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

[1] 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

[1] Sturdevant SG et al. Contemp Clin Trials Commun. 2021;22:100746 (Goldilocks approach and app)
[2] 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 1st 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 1st ICU HO-MRSA culture, MRSA BSI, any BSI

[1] Huang SS et al. NEJM 2013;368(24):2255-2265.

[2] Huang SS et al. NEJM 2019;380(7):638-650.

Tale of Two Trials

CLEAR Trial	REDUCE MRSA Trial
• Randomized Individuals	• Randomized hospitals
• 3y intensive recruitment	• 8-week recruitment
• Individual consent	• Waiver of informed consent
• Compensation	• No compensation
• Extensive contact/visits	• Usual hospitalization
• Intensive chart reviews	• Data from clinical warehouse
• Outcomes: 2+ years	• Outcomes + Analysis: 9 mo
• $10 million total trial	• $3 million total trial
• $4,673 per patient	• $40 per patient

[1] Huang SS et al. NEJM 2013;368(24):2255-2265.

[2] 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