Cluster randomization for Clinical Effectiveness Research

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REDUCE MRSA Trial

Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate MRSA

Funded by AHRQ DEcIDE program and
CDC Prevention Epicenters

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Cluster Randomized Trials in Comparative Effectiveness Research

Randomizing Hospitals to Test Methods for Prevention of Healthcare-Associated Infections

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Background: The need for evidence about the effectiveness of therapeutics and other medical practices has triggered new interest in methods for comparative effectiveness research.

Objective: Describe an approach to comparative effectiveness research involving cluster randomized trials in networks of hospitals, health plans, or medical practices with centralized administrative and informatics capabilities.

Research Design: We discuss the example of an ongoing cluster randomized trial to prevent methicillin-resistant *Staphylococcus aureus* (MRSA) infection in intensive care units (ICUs). The trial randomizes 45 hospitals to: (a) screening cultures of ICU admissions, followed by Contact Precautions if MRSA-positive, (b)

Results: Recruitment of hospitals is complete. Data collection will end in Summer 2011.

Conclusions: This trial takes advantage of existing personnel, procedures, infrastructure, and information systems in a large integrated hospital network to conduct a low-cost evaluation of prevention strategies under usual practice conditions. This approach is applicable to many comparative effectiveness topics in both inpatient and ambulatory settings.

Key Words: cluster randomization, comparative effectiveness, MRSA prevention

(*Med Care* 2010;48: S52–S57)

The REDUCE MRSA Cluster Randomized Trial

- Routine Care
  - Screen everyone and isolate if positive
- Targeted Decolonization
  - Screen, isolate, and decolonize if MRSA+
- Universal Decolonization
  - Stop screening, decolonize all, isolate if known MRSA+

Decolonization = chlorhexidine baths (OTC), mupirocin nasal ointment (drug)

REDUCE MRSA Trial Outcomes

- Primary Outcome
  - Any clinical MRSA isolate attributed to an ICU
  - Attributable to first ICU admission per hospitalization
- Secondary Outcomes
  - MRSA sterile site infections
  - All sterile site infections
  - MRSA resistance to mupirocin or chlorhexidine

The REDUCE MRSA Trial Setting

- 43 HCA hospitals
- 74 ICUs
- 74,000 ICU stays during 18 month intervention
- 48,000 ICU stays during 12 month baseline

Power

- Primary outcome MRSA isolate
  - 99% power to detect 40% reduction
  - Estimate from HCA baseline 20 events /10,000 days
- Secondary outcome: MRSA blood or urine culture
  - 89% power
  - Estimate from baseline 6/10,000 ICU pt days

IRB and consent process

- Centralized IRB
  - 38 hospitals ceded to lead IRB at Harvard Pilgrim Health Care
- Waiver of documented consent

IRB considerations

- Cluster randomization required for this contagious condition
- All regimens were standard of care somewhere
- Surveillance and bathing regimens not typically discussed with patients
- Anticipated favorable benefit-risk ratio

FOR YOUR INFORMATION

Our hospital is dedicated to improving medical care for its patients. We are currently participating with 44 other US hospitals in an evaluation of 3 different approaches to protect patients from highly antibiotic-resistant bacteria. All 3 approaches are already being used in many US hospitals, but it is not known whether one method is better than another. Adult intensive care units in this hospital are routinely providing ICU patients with anti-bacterial baths and nasal ointment to remove these bacteria and reduce the risk of infection in our critically ill patients.

Patients will receive daily bathing with anti-bacterial cloths and twice-a-day treatment in the nose with a topical antibiotic ointment. The cloths contain an antiseptic agent that has been used for skin cleansing in hospitals for many years and is available over the counter at your local drugstore. Both products are approved by the FDA and are extremely safe. If you have a history of sensitivity or allergy to either product, they will not be used. Data from this ICU population as a group will be used in this assessment. No individual patients will be identified.

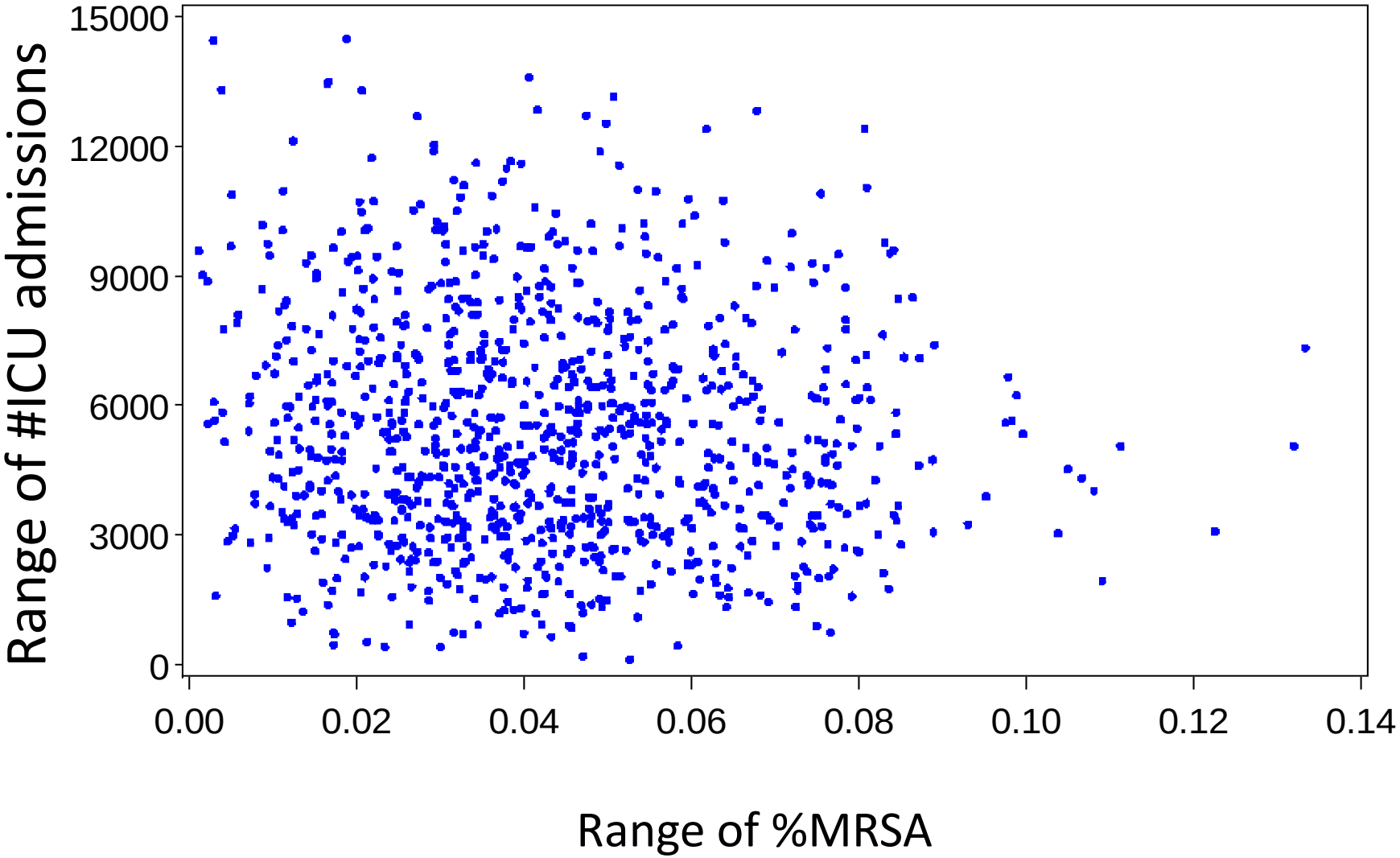
This research is funded by the national Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention. If you have a question or want additional information please talk to your nurse.

HCA AHRQ CDC

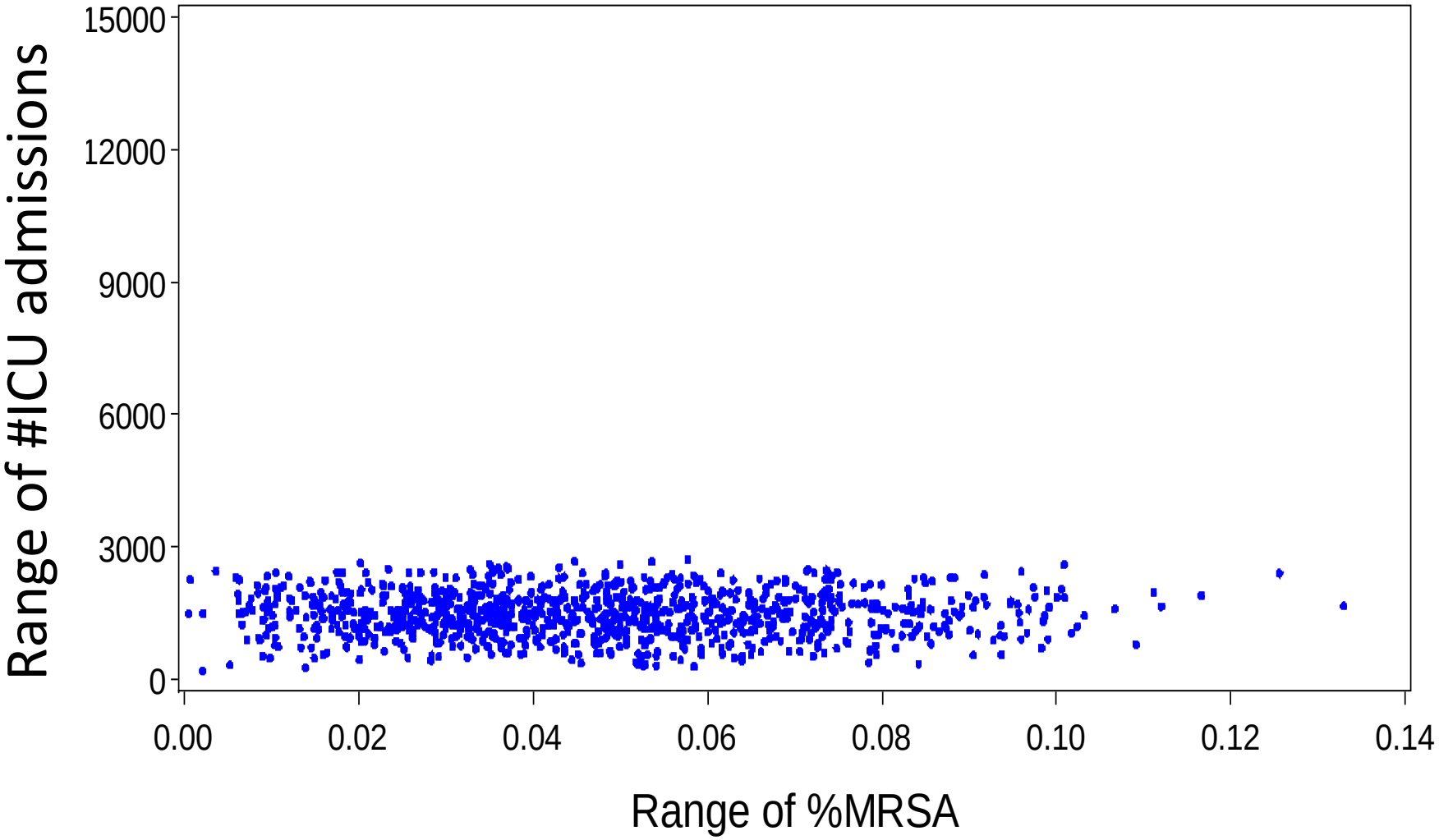
Randomization Method

- All ICUs in a single hospital randomized to same treatment
- Randomization attempted to balance
  - Hospitals' annual ICU admission volume (range 161-4,288)
  - Hospitals' baseline ICU admission MRSA prevalence (range 7-44%)

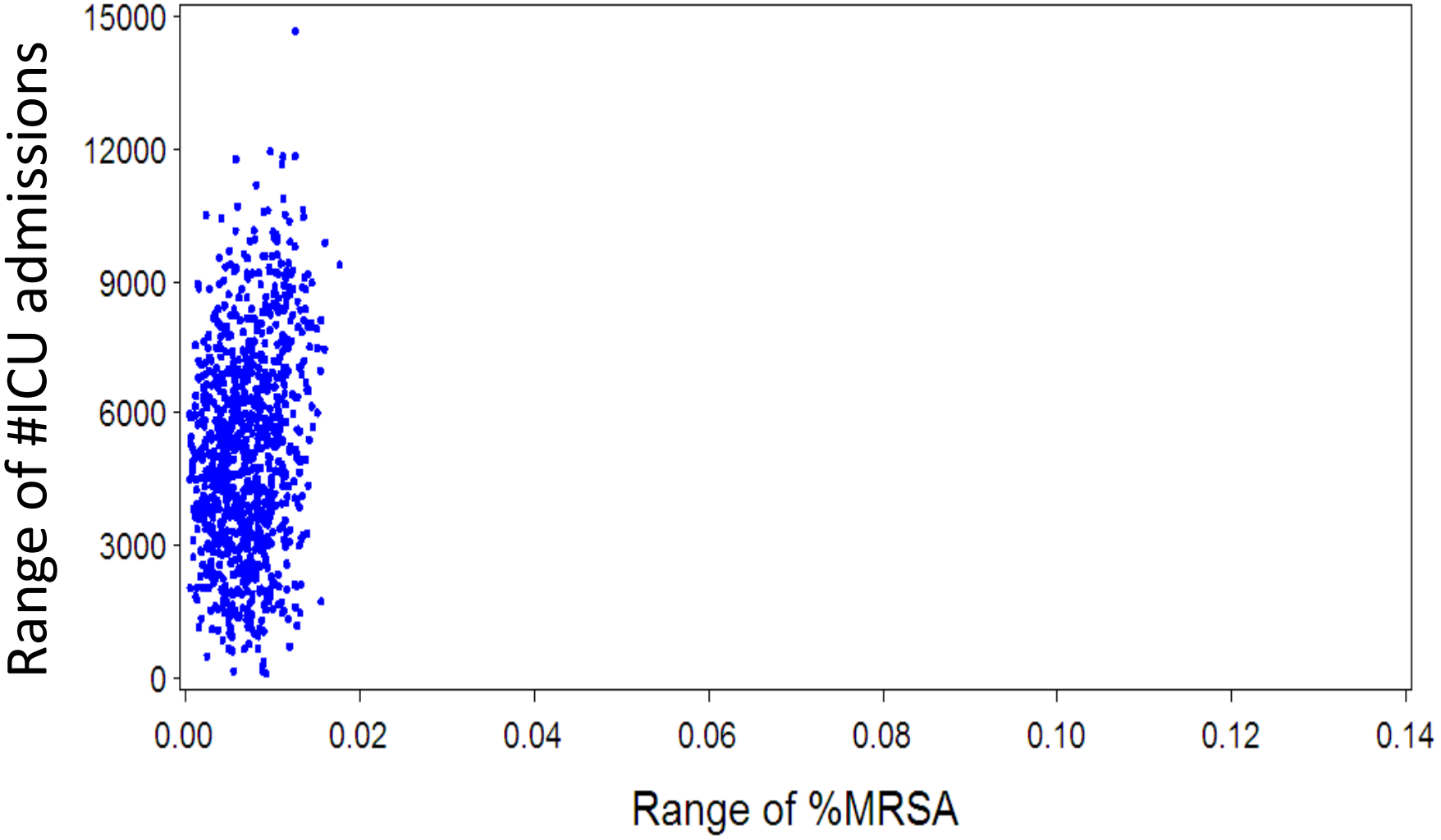
Random treatment assignment

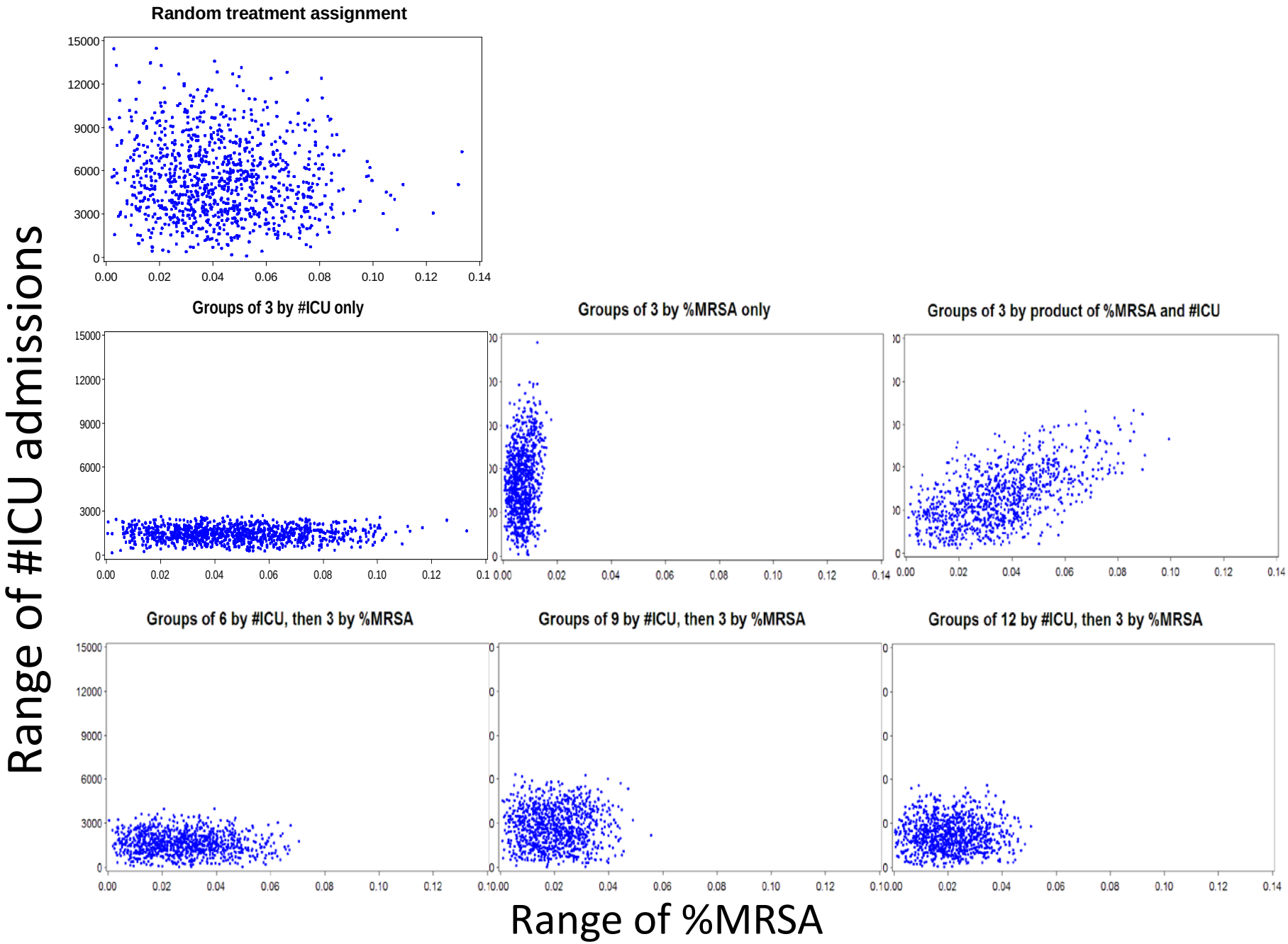


Groups of 3 by # ICU admissions only



Groups of 3 by %MRSA only




Random treatment assignment
Groups of 3 by #ICU only
Groups of 3 by %MRSA only
Groups of 3 by product of %MRSA and #ICU
Groups of 6 by #ICU, then 3 by %MRSA
Groups of 9 by #ICU, then 3 by %MRSA
Groups of 12 by #ICU, then 3 by %MRSA
Range of #ICU admissions
Range of %MRSA


Random treatment assignment
Groups of 3 by #ICU only
Groups of 3 by %MRSA only
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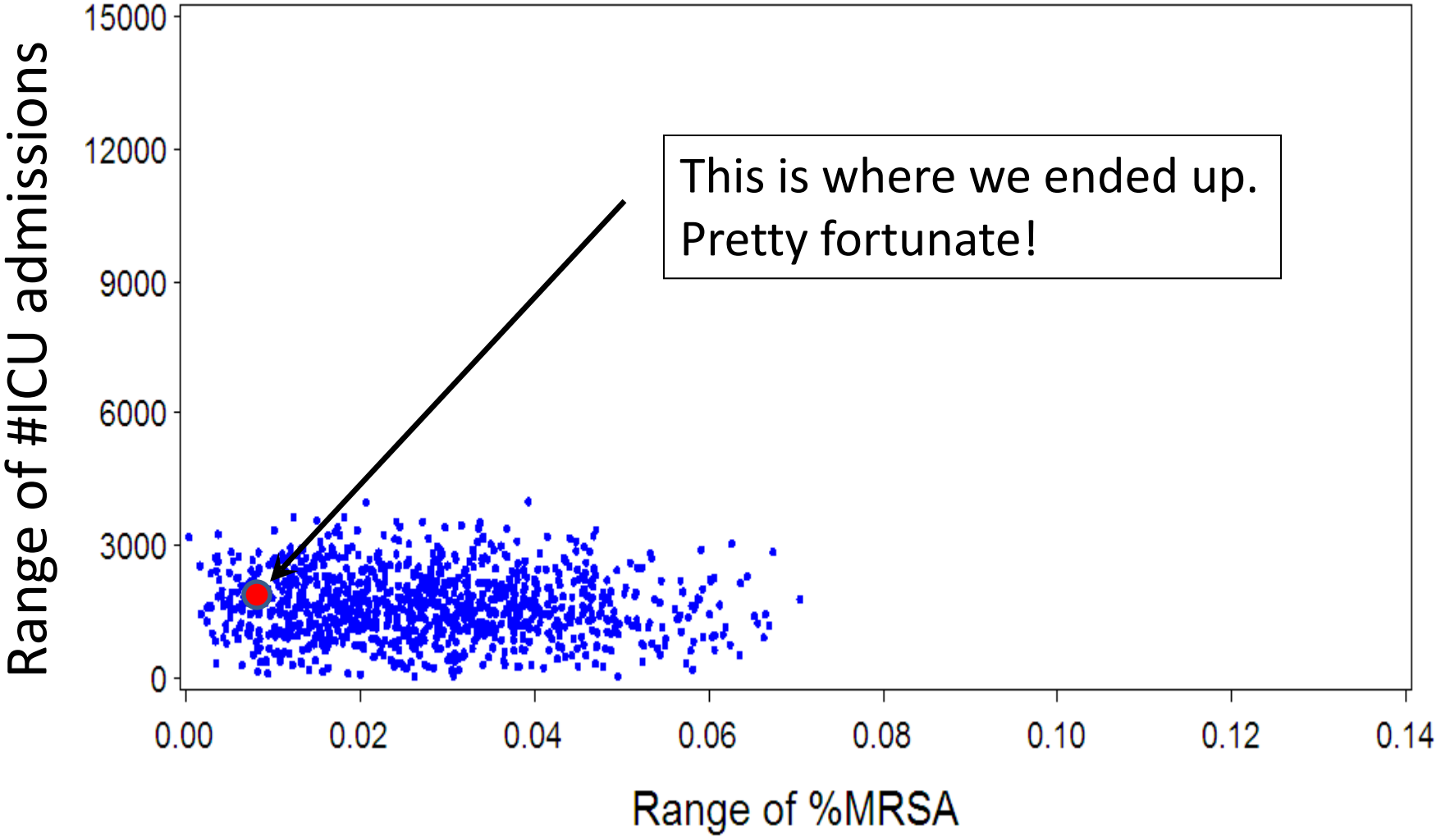
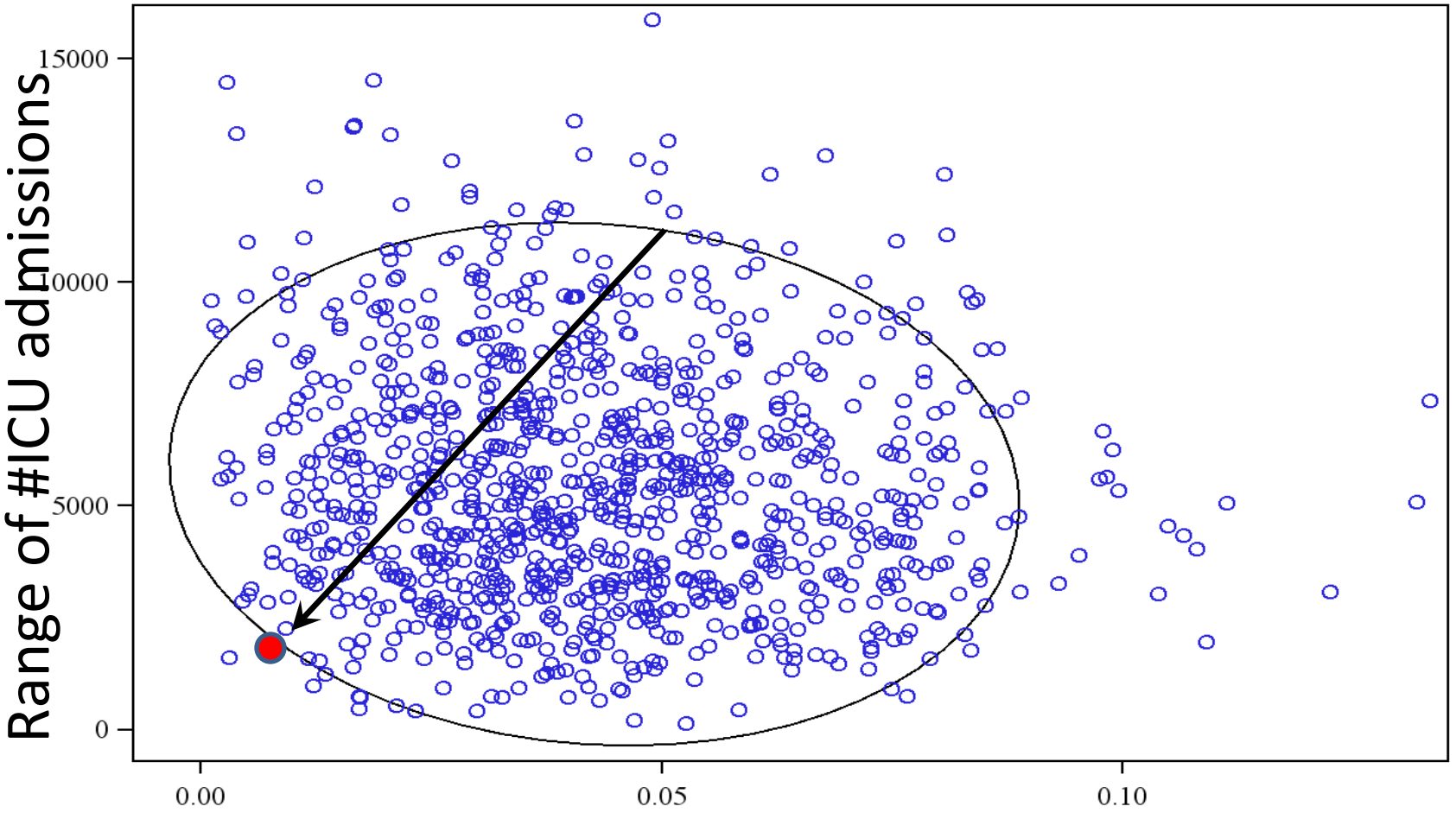


Random treatment assignment



HCA Sectors of Involvement

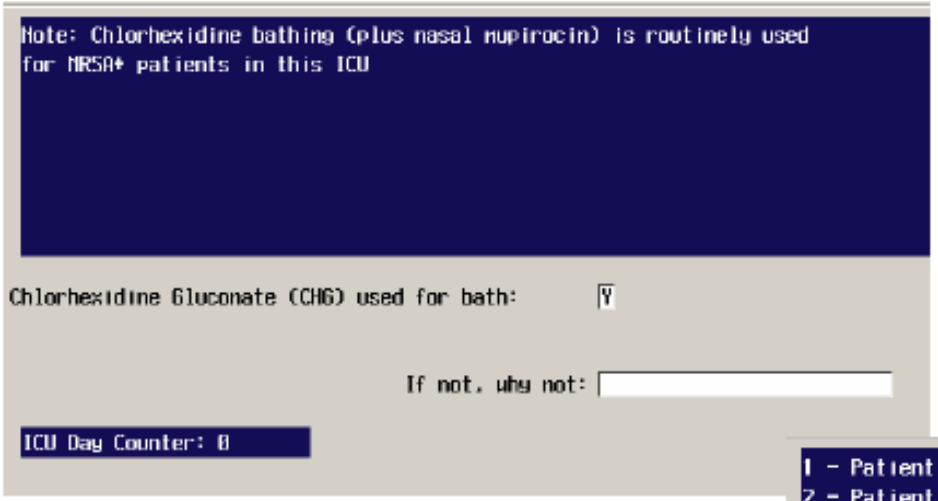
- HCA Corporate Leadership
- Division Leadership
- **Infection Prevention**
- **Quality**
- ICU Medical Directors
- ICU Directors
- IRB
- IT
- Pharmacy
- Supply Chain

Educating staff

- Unique web based training program developed for each study arm
- Each ICU unit required to complete training via the HCA Learning Management System
  - >3,600 care providers completed training
  - Continued use for new staff
- All training and materials posted for internal access

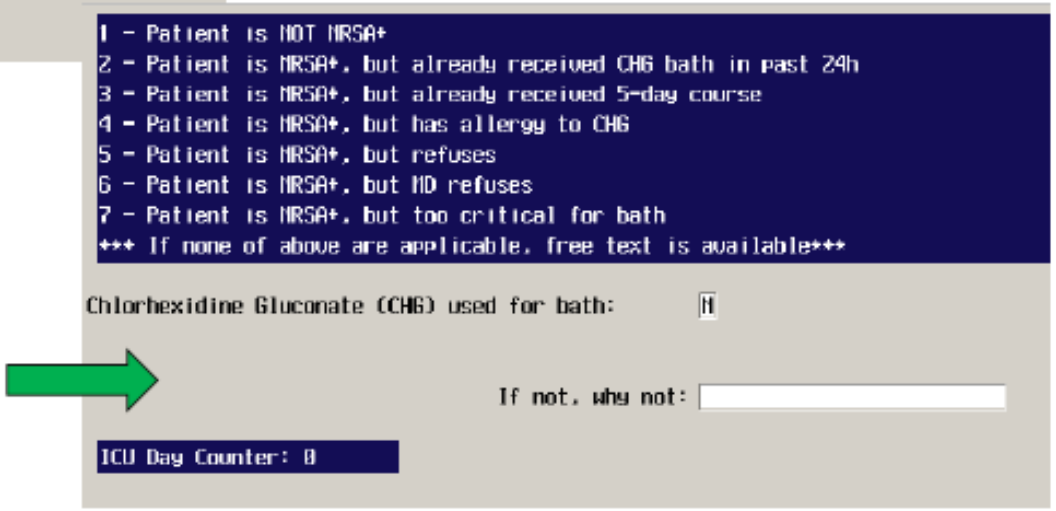
Daily Nursing Prompt for CHG Bathing Confirmation

Nursing Prompt #1



- Once a day you will complete a nursing prompt verifying if a CHG bath has occurred
- If CHG bath did **NOT** occur, make sure to complete 2nd prompt to provide a reason for not giving a CHG bath

If "Yes" – no further action required
If "No" – next prompt asks why



Nursing Prompt #2

Mission Control Duties

- Study calls
- Gmail -- Reduce.MRSA@gmail.com
- Toll free number -- (877) 294-9865
- Maintain contact information
- Study documents
- Protocol education
- Compliance reports
- Maintain log of key issues that arise
- Coordinate training and site visits
- Facilitate core groups

Resolving Potentially Conflicting Interventions

ARM 2				
Date Notified	**Status**	**Facility**	**Name of Intervention**	**Intervention Description**
1/5/2011	**Resolved**	[redacted]	Kindest Kare cleanser	Facility is currently using Steris Kindest Kare hand and body wash total body cleanser. Facility would
1/4/2011	**Resolved**		A&D Ointment	Facility wishes to switch barrier product from Calmoseptine to A&D Ointment due to corporate
11/12/2010	**Resolved**		Bioseal	Facility Cath Lab plans to use Bioseal, and patients could be sent to study ICUs.
11/11/2010	**Resolved**		CHG oral care as part of VAP bundle	Facility plan for (VAP) prevention - Oral care with CHG
10/28/2010	**Resolved**		Replace basin baths with regular bathing cloths	Facility would like to eliminate basin baths on their non- MRSA + patients and only use the regular
10/13/2010	**Resolved**		Continue incomplete CHG/Bactroban course on	Facility inquires if the 5 day CHG/Bactroban can be continued and completed on the floor when patients
10/12/2010	**Resolved**		Baby wipes with aloe	Facility would like to verify if using baby wipes containing aloe contraindicate with the trial
10/4/2010	**Resolved**		Decolonization outside of ICU	Facility did not have a protocol for routine decolonization with Bactroban on their nursing units
9/9/2010	**Resolved**		VAP	VAP protocol in possible conflict with trial elongation
9/15/2010	**Resolved**		VAMP	Facility is embarking on a project related to reducing line sepsis & a new process for drawing blood is

Centralized Data Gathering
HCA's Electronic Data Warehouse

- Person Level
  - Admissions Data
  - Charge Data
  - Nursing CHG Prompt Data
  - Lab Data
- ICU Level
  - Supply Data
  - Infection Control Reports

Analysis Plan

- Compare baseline and intervention MRSA rates
- Unadjusted comparison
- Multivariate regression model adjusting for:
  - MRSA imported into ICU,
  - length-of-stay,
  - secular trend,
  - comorbidities,
  - etc.

Cluster randomization and CER

- Pros
  - More generalizable
  - Directly tests effectiveness
  - Efficient use of routinely collected health information
- Cons(iderations)
  - Needs stakeholder engagement and buy-in
  - Views evolving regarding informed consent needs and mechanisms
  - Need to track / control concurrent changes

Health plan leaders' views

- Recognized value of CER and need for head-to-head trials
- Barriers
  - Stakeholder concerns
  - Need for budget neutrality
  - Impact on operations, e.g., formulary

Mazor. Med Care 2007;10:S29-37

Other stakeholder views

- **Members** required assurance that CRTs not compromise their care
- **Providers** concerned about potential impact on relationships with patients
- **Purchasers** needed assurances that CRT not diminish care AND that benefits be equitable

Mazor Pharmepi & Drug Safety 2009;18:554-61

Thank you