Disclaimer: The following information is fictional and is only intended for the purpose of illustrating key concepts for results data entry in the Protocol Registration and Results System (PRS).

Cluster Randomized Study Design Example

(A Phase 4, Cluster Randomized Trial Comparing Two Interventions with Standard Practice to Reduce *Poissonosis davrilarum* Infection in Intensive Care Units)

Methods

Study Design

This was a pragmatic, three-group, cluster randomized trial designed to compare strategies for preventing *Poissonosis davrilarum* (PD) infections in adult intensive care units (ICUs) in the Southern Innovative Clinical Health System (SICHS). ICUs were randomly assigned to one of three groups. All ICUs located within a hospital and all adults in those ICUs were assigned to the same group. There was a 12-month baseline period from January 31, 2016, to January 30, 2017. The 12-month intervention period immediately followed, from January 31, 2017, to January 30, 2018.

During the intervention period, each of the three groups used a different intervention strategy. Group 1, standard care, consisted of screening for PD on ICU admission and following transmission-based precaution policies (for example, ensuring appropriate use of personal protective equipment and limiting transport of patients), based on guidance from the Centers for Disease Control and Prevention (CDC). Group 2, targeted decolonization, included PD screening and transmission-based precautions like those in Group 1; in addition, PD-positive patients received a 5-day decolonization regimen of twice-daily intranasal 2% No-Bug (mupirocin) cream and daily bathing with 4% No-Scrub (hydrogen peroxide) sanitizing cloths. In Group 3, enhanced room disinfection, patients were screened for PD and health care staff used transmission-based precautions, as in Groups 1 and 2; in addition, hospital staff disinfected rooms from which PD patients were discharged with a solution containing hypochlorite (bleach) plus a disinfecting ultraviolet light (UV-C) device. Patient notices about group-specific protocols were posted in each ICU room.

The study protocol was reviewed and approved by the SICHS institutional review board. The requirement for written informed consent was waived; however, participants were required to be at least 18 years old at the time of ICU admission. All hospital record data were de-identified.

Eligibility Criteria

The inclusion criteria for participation in the study were: commitment by the hospital's administration to have all its ICUs randomized for the trial; less than 30% of patients in participating adult ICUs currently receiving either intranasal 2% No-Bug cream or 4% No-Scrub sanitizing cloths at baseline; and stable use of infection-prevention initiatives and products during the baseline period. The exclusion criterion was adoption of new infection-control initiatives that would conflict with the study protocol.

Data Sources

We obtained hospital-specific, individual patient data for ICUs from the SICHS data system for both the baseline and intervention periods. Participants with repeat visits to a hospital over the course of the study contributed data for only their first ICU visit; consequently, there were unique, nonoverlapping patients included in the analyses for these hospital ICUs during the

baseline and intervention periods. We randomized the ICUs so that the three intervention groups included a similar number of ICUs as well as a similar prevalence of PD.

The data included the unit location of each patient for each hospital day, such as an ICU or other type of room, and microbiologic data on diagnoses. We used CDC criteria to assess microbiologic outcomes and documented the first infection event per patient. PD was attributed to an ICU if the collection date fell between the start of the third day after the patient's admission to the ICU and the end of the second day after the patient's discharge from the ICU.

Statistical Analyses

The design of a cluster randomized controlled trial requires special consideration of the correlations within and between the clusters. We therefore are reporting the intracluster (intraclass) correlation coefficient (ICC), which is the proportion of the total variance of the outcome that can be explained by the variation between clusters (Campbell, Piaggio, Elbourne, & Altman, 2012), for the primary outcome analysis.

We powered this study using the rarest outcome, bloodstream infection with PD associated with a central line (i.e., a PD central line-associated bloodstream infection, or PD CLABSI). We designed the study to have 80% power to detect a moderate effect, i.e., a 40% reduction in the rate of PD infection in Group 2 and a 60% reduction in Group 3, compared with Group 1.

The primary and secondary analyses used the Cox proportional hazards regression model incorporating random effects. Unlike traditional survival regression models, this model accounts for within-cluster homogeneity in outcomes by including a random effect term for shared frailty, because the same random effect is shared by all patients within the same ICU (Rabe-Hesketh & Skrondal, 2012a & 2012b). We used the model to calculate hazard ratios comparing the baseline and intervention periods within each group as well as to compare hazard ratios across groups.

Analyses were performed with SAS 9.4 software (SAS Institute) to fit survival models to multilevel data. Level 1 represents individual patients clustered within level 2 ICUs. Our null hypothesis for each outcome was that changes in rates of infection from baseline to post-intervention would be equal across intervention groups of ICUs. If the null was rejected, we also examined pairwise comparisons among ICUs.

Results

Participants and ICUs

A total of 201 ICUs in 140 SICHS hospitals were screened for the study. Of those, 78 ICUs in 45 hospitals met the inclusion criteria and were randomized (Figure 1). However, four ICUs were excluded from the study because, before the baseline period, the hospitals in which they were located implemented new infection-control programs that would have interfered with the study protocol. Two ICUs in Group 2 withdrew during the intervention period. The baseline period and the intervention period each lasted 12 months.

A total of 236,931 participants were evaluated for the study during the baseline and intervention periods (Table 1). Patient characteristics were not significantly different across randomization groups or between the baseline and intervention periods in any arm.

Figure 1. Recruitment, enrollment, and progression of the study population

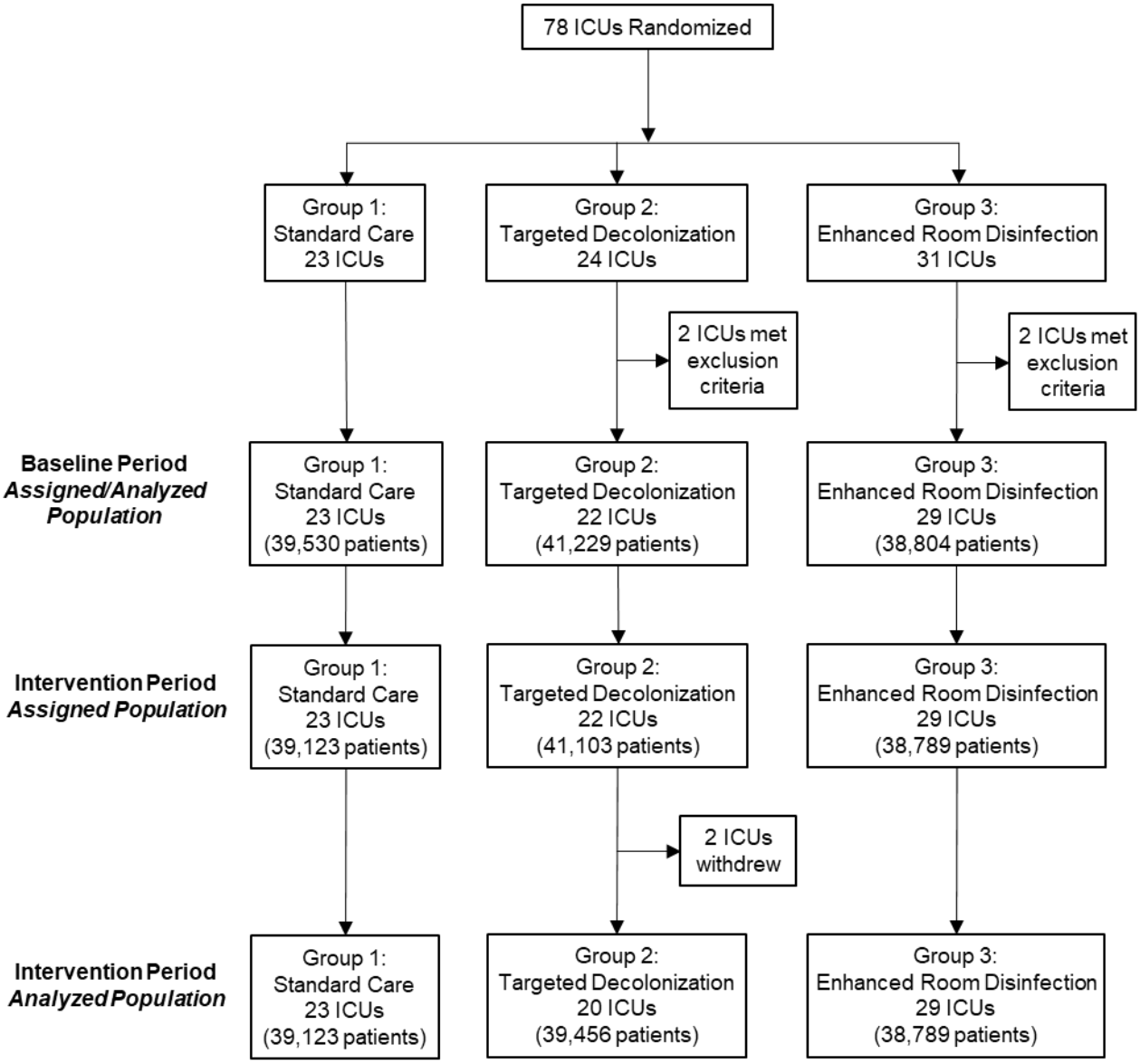

Table 1. Characteristics of patients and ICUs by intervention group for baseline and intervention periods. Group 1: Standard Care; Group 2: Targeted decolonization; Group 3: Enhanced room disinfection

Variable	12-Month Baseline Period				12-Month Intervention Period			
	Group 1	Group 2	Group 3	Total	Group 1	Group 2	Group 3	Total
ICUs *(number)*	23	22	29	74	23	20	29	72
ICU type (*number of ICUs*)								
Medical only	3	3	2	8	3	1	2	6
Surgical only	2	4	3	9	2	4	3	9
Medical and surgical	18	15	24	57	18	15	24	57
Admission with ICU stay *(number of patients)*	39,530	41,229	38,804	119,563	39,123	39,456	38,789	117,368
Age in years (*median and interquartile range)*	63 (51–76)	66 (54–78)	67 (55–79)	65 (52–77)	64 (52–77)	65 (53–77)	66 (54–78)	65 (52–77)
Sex (*number and percentage of patients*)								
Female	19,014 (48.1)	20,367 (49.4)	20,100 (51.8)	59,481 (49.7)	18,427 (47.1)	19,412 (49.2)	18,929 (48.8)	56,768 (48.4)
Male	20,516 (51.9)	20,862 (50.6)	18,704 (48.2)	60,082 (50.3)	20,696 (52.9)	20,044 (50.8)	19,860 (51.2)	60,600 (51.6)
Prior PD infection* (*no. of patients)*	3,826	4,025	3,911	11,762	4,951	4,783	4,112	13,846
Race (*number and percentage of patients*)								
American Indian/ Alaska Native	420 (1.1)	859 (2.1)	560 (1.4)	1,839 (1.5)	391 (1.0)	659 (1.7)	581 (1.5)	1,631 (1.4)
Asian	1,962 (5.0)	1,209 (2.9)	2,737 (7.1)	5,908 (4.9)	1,956 (5.0)	1,009 (2.6)	2,715 (7.0)	5,680 (4.8)
Black or African American	8,386 (21.2)	9,882 (24.0)	9,821 (25.3)	28,089 (23.5)	8,215 (21.0)	9,182 (23.3)	9,697 (25.0)	27,094 (23.1)
Native Hawaiian or Other Pacific Islander	131 (0.3)	244 (0.6)	169 (0.4)	544 (0.5)	129 (0.3)	158 (0.4)	171 (0.4)	458 (0.4)
White	28,631 (72.4)	29,035 (70.4)	25,517 (65.8)	83,183 (69.6)	28,432 (72.7)	28,448 (72.1)	25,625 (66.1)	82,505 (70.3)
Ethnicity (*number and percentage of patients*)								
Hispanic or Latino	910 (2.3)	985 (2.4)	1,501 (3.9)	3,396 (2.8)	896 (2.3)	963 (2.4)	1,479 (3.8)	3,338 (2.8)
Not Hispanic or Latino	38,620 (97.7)	40,244 (97.6)	37,303 (96.1)	116,167 (97.2)	38,227 (97.7)	38,493 (97.6)	37,310 (96.2)	114,030 (97.2)

* One year prior to admission through day 2 of ICU stay

Outcomes

Outcome variables were monitored and recorded for both the 12-month baseline period and the 12-month intervention period for each ICU.

Primary Outcome

The primary outcome was the number of events and incidence rate of confirmed ICU-attributable, PD-positive clinical cultures in each group (Table 2). Cultures were collected daily beginning the third day after ICU admission through the second day after discharge. Confirmed infections included any positive cultures collected from skin or mucosal surfaces and polymerase chain reaction (PCR)-verified bloodstream infections (BSIs). Incidence rate was defined as the number of new events per 1,000 ICU-attributable patient-days at risk for the event. For the baseline period, the total ICU-attributable patient-days were 64,532 for Group 1, 58,547 for Group 2, and 70,521 for Group 3. For the intervention period, the total ICU-attributable patient-days were 58,740 for Group 1, 61,325 for Group 2, and 66,401 for Group 3.

Secondary Outcomes

We analyzed two secondary outcomes: the number of events and incidence rate of new BSIs with any pathogen, including PD, and the number of events and incidence rate of new PD CLABSIs (Table 2). BSI was based on the first eligible infection by any pathogen per patient; therefore, a patient with more than one ICU-associated infection was counted only once. Pathogens were any gram-positive organism, gram-negative organism, or *Candida* species confirmed by a laboratory culture in a sample collected from the third day after ICU admission through the second day after discharge. PD CLABSI was a primary BSI in a patient who had a central line within the 48-hour period before the development of the BSI.

Table 2. Numbers of events and incidence rates of *Poissonosis davrilarum* infections and other outcomes by intervention group, for the baseline and intervention periods.

Outcome	Group 1: Standard Care		Group 2: Targeted Decolonization		Group 3: Enhanced Room Disinfection	
	Baseline	Intervention	Baseline	Intervention	Baseline	Intervention
ICU-attributable PD infections *(number and incidence rate*)*	215 (3.3)	178 (3.0)	240 (4.1)	199 (3.2)	249 (3.5)	143 (2.2)
BSIs with any pathogen *(number and incidence rate*)*	251 (3.9)	225 (3.8)	269 (4.8)	229 (3.7)	413 (6.1)	220 (3.3)
PD CLABSIs *(number and incidence rate*)*	45 (0.7)	55 (0.9)	47 (0.8)	61 (1.0)	101 (1.4)	60 (0.9)

* Patient-days after each event were excluded from the analysis; therefore, denominators are different for each cell and are not reported.

Hazard ratios and 95% confidence intervals for the three outcomes, by intervention group, are shown in Table 3, with the overall p-value for the differences among groups for those outcomes. Pairwise comparisons found that the difference between the hazard ratios for Group 1, the standard care group, and Group 2, the targeted decolonization group, approached significance (p = 0.09) for the primary outcome of ICU-attributable PD infection. The hazard ratio for Group 3, the enhanced room disinfection group, compared with the standard care group, was significantly lower (p = 0.003) for the primary outcome. The ICC for clusters for the primary outcome was 0.298.

Pairwise comparisons for the secondary outcome of BSI with any pathogen found a significantly lower hazard ratio for Group 3, compared with both Group 1 (p < 0.001) and Group 2 (p = 0.04). Pairwise comparisons were not made for the secondary outcome of PD CLABSI because the overall p-value was not found to be significant.

Table 3. Hazard ratios and 95% confidence intervals for *Poissonosis davrilarum* (PD) infections and other outcomes, by intervention group

Outcome	Group 1: Standard Care	Group 2: Targeted Decolonization	Group 3: Enhanced Room Disinfection	Overall p-value*
ICU-attributable PD infection†	0.92 (0.77–1.10)	0.77 (0.64–0.92)	0.63 (0.53–0.74)	0.01
BSI with any pathogen‡	0.97 (0.83–1.14)	0.77 (0.65–0.90)	0.55 (0.48–0.62)	< 0.001
PD CLABSI	1.22 (0.80–1.79)	1.20 (0.81–2.01)	0.70 (0.47–1.02)	0.08

* Test of all three intervention groups being equal
† Pairwise analyses: Group 2 vs. Group 1, p = 0.09; Group 3 vs. Group 1, p = 0.003; Group 3 vs. Group 2, p = 0.16
‡ Pairwise analyses: Group 2 vs. Group 1, p = 0.05; Group 3 vs. Group 1, p < 0.001; Group 3 vs. Group 2, p = 0.04

Adverse Events

We collected data on four anticipated adverse events (AEs) during the 12-month intervention period. AEs that may have been attributed to 4% No-Scrub sanitizing cloths or intranasal 2% No-Bug cream, including pruritus and intranasal rash, were systematically collected for Group 2 (the only participants who received those treatments) through a review of patient records from 3 days after ICU intake through 2 days after ICU discharge (Table 4). We also collected data on the incidence of sepsis, anaphylaxis, and deaths in the ICU attributed to BSI during the same period (also shown in Table 4). No other deaths were reported.

Table 4. Systematically collected anticipated and attributable adverse events during the intervention period, *Poissonosis davrilarum* (PD) Infection Study

Description	Group 1: Standard Care	Group 2: Targeted Decolonization	Group 3: Enhanced Room Disinfection
Admission with ICU stay *(no. of patients)*	39,123	39,456	38,789
Deaths in ICU from BSI	27	28	26
Serious adverse events *(total)*	182	187	186
Sepsis	180	187	183
Anaphylaxis	2	0	3
Non-serious adverse events *(total)*	NA	22	NA
Pruritus	NA	15	NA
Intranasal rash	NA	7	NA

NA = Not applicable. Non-serious adverse events were not assessed in Group 1 or 3.
Note: The Medical Dictionary for Regulatory Activities (MedDRA), version 12.0 was used for this analysis.

References

Campbell, M. K., Piaggio, G., Elbourne, D. R., & Altman, D. G. (2012). Consort 2010 statement: extension to cluster randomised trials. *BMJ*, *345*, e5661.

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