Duke Center for
Antimicrobial Stewardship
and Infection Prevention

Early Recognition and Response to Increases in Surgical Site Infections using Optimized Statistical Process Control Charts

The Early 2RIS Study

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STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the applicable principles and regulatory requirements from the United States Code of Federal Regulations (CFR), including 21 CFR 56 (institutional review board [IRB]) and 21 CFR 50 (informed consent) and to the principles outlined in applicable ICH guidelines.

STUDY PRINCIPAL INVESTIGATOR SIGNATURE

The signature below documents the review and approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. federal regulations and ICH guidelines.

Deverick Anderson, MD, MPH

Study Principal Investigator

Signature

1/26/17

Date

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LIST OF ABBREVIATIONS

DICON	Duke Infection Control Outreach Network
EWMA	Exponentially-weighted moving average
HAI	Healthcare-associated infection
IP	Infection preventionist
MA	Moving average
NHSN	National Healthcare Safety Network
SPC	Statistical process control
SSI	Surgical site infection

PROTOCOL UPDATES

Version	Date	Notes
1.0	3-1-17	Original approved protocol
2.0	5-17-17	Updated objectives, hypotheses, statistical section
2.1	4-17-18	Eliminated typo from objectives; corrected Schematic/Description of Study Design

PROTOCOL SYNOPSIS

Protocol Title:	**Early Recognition and Response to Increases in Surgical Site Infections using Optimized Statistical Process Control Charts**
Phase:	Not Applicable
Products:	Not Applicable
Objectives:	To measure the effectiveness of surveillance using optimized SPC methods and feedback on rates of SSI compared to traditional surveillance and feedback
Study Design:	Multicenter, stepped wedge cluster randomized trial
Study Population:	Patients undergoing one of targeted surgical procedures at 29 DICON hospitals
Number of Participants:	Patients undergoing >250,000 targeted surgical procedures over a 4-year study period
Number of Sites:	29
Duration of Participant Participation:	4 years (12 months of baseline and 3 years of active intervention)
Dose Schedule:	Not Applicable
Estimated Start:	March 1, 2017 (for active intervention)
Estimated Time to Complete Enrollment:	4 years

Schematic/Description of Study Design

SSI surveillance and feedback for surgical procedure clusters during the multicenter, stepped wedge cluster randomized trial

	Time Period												
Randomization Group	**B**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
1 (n=9)													
2 (n=9)													
3 (n=8)													
4 (n=9)													
5 (n=8)													
6 (n=8)													
7 (n=10)													
8 (n=9)													
9 (n=9)													
10 (n=10)													
11 (n=8)													
12 (n=8)													

B=baseline period (1 year); Other periods=3 months

Blue=traditional surveillance, during which hospitals will receive routine SSI surveillance data reports distributed biannually. In addition, observed increases

White=intervention, during which hospital clusters will received feedback from traditional surveillance and signals generated by applying optimized SPC methods to SSI surveillance data

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Surgical site infections (SSIs) are the most common and costly healthcare-associated infections (HAI) in the US.[1-4] More than 150,000 patients acquire a SSI each year and suffer from adverse outcomes, including longer hospitalizations and increased mortality.[5-7] In total, SSIs cost the US healthcare system more than $3 billion annually.[4,8] Over the past decade, hospitals across the US have spent considerable time and resources optimizing SSI prevention processes. While most hospitals have greatly improved compliance with important process measures, increased compliance has not led to decreased rates of SSI.[9,10] As a result, **innovative strategies to prevent SSI are greatly needed.**

Feedback of SSI data to surgical personnel is a cornerstone of SSI prevention[11] and is well proven to lead to lower rates of SSI.[12-15] Traditional surveillance monitors rates of SSI following common surgical procedures, often calculated on a quarterly or biannual basis. Traditional statistical methods require aggregation of measurements over time, which can delay and limit analysis;[16] therefore, changes in SSI rates often are detected several months after the rate first changed, if detected at all.

Statistical process control (SPC) is an analytic approach that combines time series analysis methods with graphical presentation of data to determine whether a process or rate exhibits "common cause" natural variation or "special cause" unnatural variation due to circumstances that have not previously been inherent in the process.[17] In other words, SPC methods help separate "noise" from a true signal. Commonly employed in manufacturing and other industries, SPC methods have emerged as useful tools for identifying and analyzing changes in HAI.[18-21] To date, however, SPC methods are not commonly utilized in a rigorous manner to provide real-time surveillance of HAIs such as SSIs.

2.2 Scientific Rationale

Few strategies for prevention of SSI are rigorously evidence-based. Only 7 of the 15 basic practices for preventing SSI (and 9 of the 24 recommendations overall) were categorized as "High" quality of evidence in the most recent SHEA/IDSA compendium on "Strategies to Prevent SSI in Acute Care Hospitals: Update 2014."[22] Studies designed to evaluate strategies for SSI prevention have suffered from poor methodology that limits the generalizability of findings, including data from single centers and/or the use of before-after study designs that are prone to bias. Finally, while collaborative improvement projects can be used to promote SSI prevention, these collaboratives are designed to improve implementation, not evaluate efficacy and/or effectiveness.[23,24]

Traditional SSI surveillance is limited. One evidence-based basic practice is SSI surveillance and feedback to surgical personnel, a cornerstone of SSI prevention since the SENIC study was published in 1985.[11] Indeed, the feedback of surveillance data to surgeons has repeatedly been shown to improve surgical patient outcomes, including SSI.[12-15] Traditional SSI surveillance at individual hospitals involves a multi-step process: data collection, rate calculation (typically on a quarterly or semiannual basis), and feedback. Rates can be compared to previous rates at the hospital and/or to external benchmarks, such as those established by the NHSN[25] or programs like the National Surgical Quality Improvement Project (NSQIP).

The traditional approach for SSI surveillance and feedback has several major deficiencies because SSI is a low-frequency event. First, the traditional approach is slow. Traditional statistical methods require aggregation of measurements over time, which delays analysis until enough data accumulate.[16] In practice, hospital epidemiologists are often ***told*** about a problem (e.g., from a perceptive surgeon) rather than discovering the problem via ongoing "real-time" data analysis. Second, traditional statistical tests and resulting p-values are difficult to interpret. Thus, standard analytic methods that compare average SSI rates between arbitrarily designated time intervals will not identify a statistically significant problem unless the "signal" is very strong. Third, analyses based on average SSI rates during predefined time periods have limited ability to rapidly identify important, real-time trends. For example, a cluster of SSIs may occur during one month, but this "signal" could be diluted by accrual of additional data in subsequent months prior to the next scheduled analysis. Finally, the use of external benchmarks such as NHSN or NSQIP is challenging because of cost, delayed reports, use of historical data, lack of feedback of actionable items, and concentration on a few, specific procedures. ***Statistical process control (SPC) methods specifically address and overcome all of these deficiencies.***

Summary. SSIs are now the most common and costly HAI in US healthcare and lead to significant patient suffering. Efforts to decrease SSI fall directly in line with one of AHRQ's four priority areas of focus: "To make healthcare safer." Because current, widely used strategies for SSI prevention are of increasingly uncertain or unproven effectiveness, **innovative strategies and studies to prevent SSI using rigorous methodological design are greatly needed.**

This quality improvement study will seek to use a standard intervention for SSI prevention (i.e., surveillance and feedback) to decrease the risk of SSI. We will compare two strategies for surveillance and feedback, standard methods vs. SPC methods.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

We consider this quality improvement project to be a minimal risk study. The only potential risk would be loss of confidentiality. We believe this risk will be extremely low. The data used in this study will primarily be obtained from the DICON Surgical Site Database, a limited dataset housed behind the Duke IT firewall. While dates are included in this dataset, no other patient identifiers are included. Dates are included in this database in order to trend incidence, identify clusters/outbreaks, and determine outcomes (length of hospitalization) during the course of regular DICON operations. All patients are identified through a DICON ID number. Study personnel are unable to link the DICON ID number to any other patient identifiers. Use of this database for other types of research has previously been approved by the Duke University Health System IRB (**Pro00050488**, Protocol for Research using Limited Datasets in the Duke Infection Control Outreach Network (DICON) Surveillance and Surgical Site Databases).

All participating hospitals are members of DICON. DICON hospitals have Business Agreement Arrangements (BAA) in place that outline our interactions with hospitals. These interactions will not change as part of this study. In brief and per the routine outlined in the BAAs, in the event that an increase in SSI is identified during the study (either by routine surveillance or by optimized SPC charts), DICON personnel will contact local infection prevention personnel to characterize and jointly formulate a response to the increase. At no point will study personnel have access to other patient identifiers such as MRN or date of birth.

2.3.2 Benefits

Patients may benefit from this study if our intervention, the use of optimized SPC charts, leads to a decrease in the risk of SSI. More specifically, if a patient undergoes a surgical procedure at a hospital randomized to intervention, the patient may have a lower risk of SSI.

3 OBJECTIVES

The purpose of this quality improvement study is to measure the effectiveness of surveillance using optimized SPC methods and feedback on rates of SSI compared to traditional surveillance and feedback.

For our analyses, we will use the following definitions:

1. Signal – Alert created that an important increase in SSI has been detected. Signals can be generated by SPC charts or by standard surveillance methods. A "true positive" signal is any signal that requires further investigation.
2. Investigation – After review of basic information regarding the signal, study investigators gather additional data from the DICON database to determine if an investigation is required.
3. Intervention – After the preliminary investigation, study investigators begin the process of providing feedback about the signal and preliminary investigation.

Using these definitions, several important outcomes can be measured and compared between surveillance strategies, including

1. The number of signals generated by each type of surveillance strategy
    a. All clusters, for 3-year post-baseline period
2. The proportion of signals for which investigation was recommended
    a. This proportion will be used to determine the number of "true positive" and "false positive". These values will be used to calculate the positive predictive value of the surveillance strategy
3. The true number of positive signals will be calculated by combining the number of true positive results from each surveillance strategy. For example, if SPC identifies 15 true positive signals and standard surveillance identified 5 (yet 3 were also identified by SPC), then true number of positive signals would be 17. After this number is calculated, we will calculate the sensitivity for each strategy (15/17=88% for SPC and 5/17=29% for standard in this example).
4. Number of signals for which intervention was performed
    a. Due to the blinded nature of the study, signals and signal adjudication (ie, investigation or not) will be collected for all clusters for the 3-year post-baseline period. That is, signals generated by either method will be documented and, if necessary, investigated. However, interventions will only be performed based on the source of the signal (SPC vs. standard surveillance) and randomization scheme. For signals generated via SPC randomized to standard surveillance, no interventions will be performed. Thus, the proportion of signals that led to investigation will only be calculable for SPC methods from the clusters randomized to intervention. However, this proportion will be calculable for all signals generated by standard surveillance regardless of randomization scheme. However, for the purpose of comparing these proportions between surveillance strategies, we will limit the analysis to the period during which each cluster was randomized to intervention.
5. Dates of signal generation will be documented for all signals, regardless of surveillance method. For months in which true positive signals were generated by both methods, we will calculate the number of days between generation of the signals from each type of method. If generated on the same day, the value will be "0". Otherwise, this value will be calculated by subtracting the date of optimized SPC method signal generation from the date of traditional surveillance signal generation (e.g., 1/31/2017 – 1/11/2014 = 20 days). A positive value means that the optimized SPC method identified the signal prior

to the traditional surveillance method; a negative value means the traditional surveillance method identified the signal prior to the optimized SPC method.

During investigations, several steps will be taken and documented. For investigations that involve review of line listings of patients with SSI, each will be provided a "preventability score" after reviewing if best practices were followed. The preventability score will be calculated by determining the proportion of best practices followed during the procedure.

3.1 Study Hypotheses and Objectives

3.1.1 Hypotheses

Primary Hypothesis

Hospital clusters that receive feedback on rates of SSI using optimized SPC methods and traditional surveillance methods will have lower rates of SSI compared to hospital clusters that receive feedback from traditional surveillance methods alone.

Secondary Hypotheses

1. Hospital clusters that receive feedback on rates of SSI using optimized SPC methods and traditional surveillance methods will have lower rates of superficial-incisional and complex SSI compared to hospital clusters that receive feedback from traditional surveillance methods alone
2. The rate of signals generated by optimized SPC methods will be higher than the rate generated by traditional surveillance.
3. Signals generated by optimized SPC methods will have higher sensitivity to identify important increases in SSI rates (defined as signals that lead to investigations) compared to traditional surveillance.
4. Signals generated by optimized SPC methods will have lower positive predictive value to identify important increases in SSI rates (defined above) compared to traditional surveillance.
5. Among clusters for which true positive signals are generated by both methods, signals generated by optimized SPC methods will be identified prior to signals generated by traditional surveillance methods.

3.1.2 Primary Objective

1. To determine if hospital clusters randomized to receiving feedback from optimized SPC methods collectively have lower rates of SSI compared to hospital clusters randomized to receiving feedback from traditional surveillance methods

3.1.3 Secondary Objectives

1. To determine if hospital clusters randomized to receiving feedback from optimized SPC methods collectively have lower rates of superficial-incisional, deep-incisional, organ/space, and/or complex SSIs compared to hospital clusters randomized to receiving feedback from traditional surveillance methods. (corresponds to secondary hypothesis 1.)
2. To determine and compare the number of signals identified using optimized SPC methods and traditional surveillance methods over the three-year post-baseline period. (Corresponds to secondary hypothesis 2.)

    a. Descriptive – overall numbers; then summarize per cluster per month
    b. For comparison – develop standardized rate, likely number of signals/100 procedures performed
3. To estimate and compare the proportion of signals that led to investigations using optimized SPC methods and traditional surveillance methods, including the number of true positive signals, false positive signals, positive predictive value, and sensitivity of each method. (Corresponds to secondary hypotheses 3 and 4.)
4. To summarize the time to completion of interventions, calculated as the time from signal identification to close of the intervention (in days).
5. To summarize the preventability score for SSIs reviewed during the study.
6. To compare the timing of true positive signal identification between the two surveillance strategies (Corresponds to secondary hypothesis 5).
    a. Average time between signals
7. Proportion of true positive signals in which optimized SPC methods found the signal first.

4 STUDY DESIGN

The Early 2RIS study will be a prospective, multicenter cluster randomized controlled trial using stepped wedge design. The active component of the quality improvement study will be performed in 29 DICON hospitals over three years, from March 2017 through February 2020.

4.1 Study Population

4.1.1 Selection of the Study Population

All study hospitals participate in DICON (http://dicon.medicine.duke.edu/). DICON is a network of 43 community hospitals in North Carolina, South Carolina, Georgia, and Virginia that provides community hospitals access to consultative services from infection prevention experts, data analyses and benchmarking, and educational materials designed by faculty from Duke. Each site has a contract (Infection Prevention Program Development Services Agreement) with Duke, which includes a data use agreement (DUA) and business agreement (BAA). Routine network activities, including regular visits by the DICON liaison nurse, data reports, and education, will continue throughout the study. All participating hospitals submitted letters of support for inclusion in the study.

4.1.2 Inclusion/Exclusion Criteria

Inclusion criteria: All patients who undergo one of 13 targeted procedures at 29 study hospitals will be included in the analysis (Table 1). These procedures were selected because they are frequently performed in community hospitals and/or are associated with particularly adverse outcomes if complicated by SSI. Eligible procedures will be categorized by procedure type at each hospital using ICD9 codes published by the NHSN.[26] Clusters were constructed to ensure that surgeons who perform similar types of procedures were grouped together to limit potential bias. *These clusters are the units for randomization and analysis*.

Table 1. Procedures include in each cluster.

Cluster	Procedure
Cardiac	Coronary artery bypass graft Cardiac valve replacement
GI	Colon Herniorrhapy
Joint	Knee arthroplasty Hip arthroplasty
OB-GYN	Cesarean section Hysterectomy Vaginal hysterectomy
Spine	Spinal fusion Laminectomy
Vascular	Carotid endarterectomy Peripheral venous bypass

Exclusion criteria: DICON hospitals that did not submit a letter of support for participating in the study will be excluded. Patients not undergoing one of these 13 procedure types at the 29 study hospitals will be excluded from the analysis.

4.1.3 Treatment Assignment Procedures

Randomization will occur at the cluster level within hospitals. One cluster within each hospital will be randomized to receive the optimized SPC feedback intervention in real time during each post-baseline 3-month "step" (Table 2). The rest of the clusters will continue to receive standard, traditional feedback. Once randomized to intervention, clusters will receive feedback from optimized SPC methods **and** standard feedback for the remainder of the study. There will be 12 steps in total (equal to the maximum number of clusters per hospital). At the last step, the remaining cluster within each hospital will begin the intervention.

Table 2. Stepped wedge design schematic

	Time Period						
Randomization Group	**B**	**1**	**2**	**3**	**4**	**…**	**12**
1 (n=9)							
2 (n=9)							
3 (n=9)							
4 (n=9)							
… (n=9)							
12 (n=8)							

B=baseline period (1 year); Other periods=3 months
Grey=traditional surveillance; White=intervention

4.1.4 Strategy Descriptions

As per DICON standard operating procedure, local personnel in all study hospitals and clusters will receive biannual reports with bar graphs, analyses generated using standard statistical methods, and data interpretation.

Intervention Cluster – Data entered locally by infection preventionists at DICON hospitals are immediately transmitted to the DICON Surgical Database. Data submitted to the DICON Surgical Database automatically undergo immediate analysis by optimized SPC methods. If a signal is generated, study personnel in DICON will be notified to adjudicate the signal and determine if further action is required.

Table 3. Sensitivity and specificity of optimized SPC methods

Chart	DICON baseline	Window size	Window lag	Avg param	Control limits	Chart type	Sens	Spec	PPV	NPV
A	Yes	18	6	12	1	MA	0.88-090	0.67-0.75	0.56-0.65	0.93-0.94
B	No	3	3	6	1	MA				

Optimized SPC methods include a logical disjunction of 2 different variations of moving average charts (i.e., signals are generated whenever either chart features an out-of-control point). **Chart A** evaluates local SSI rates against medium-term historical SSI rates (18-month reference period with a 6-month lag) for the same procedure type across all other DICON hospitals, and aggregates these differences using a 12-month moving average. **Chart B** contrasts current SSI rates against the recent past at the same hospital (3-month baseline interval with a 3-month lag), then averages these differences over the prior 6 months. Therefore, while the former chart can detect long-term divergences between local and DICON SSI rates, the latter is able to identify sustained, short-term local increases in SSI incidence, irrespective of their relationship to the overall DICON rate. Both charts employ a relatively low control limit of 1 standard deviation, and are thereby tuned for screening potential signals rather than detection of definite signals (and rejection of unlikely outbreaks). Correspondingly, this specific chart combination reached sensitivities of 0.9 and 0.88, and specificities of 0.67 and 0.75, on the training and validation subsets, respectively (Table 3).

Control Cluster – Local personnel in clusters randomized to traditional surveillance and feedback will receive bar graph reports and data interpretation per routine DICON surveillance described above.

In the event that an important increase in SSI is detected by standard surveillance (regardless of cluster), DICON personnel will investigate the increase with local personnel as per routine DICON practices.

4.1.5 Termination of Study

This study may be terminated at any time by the principal investigator (PI) in consultation with the AHRQ. Otherwise, the study will be terminated at the end of enrollment, analysis, and publication of findings.

5 STUDY PROCEDURES

5.1 Data Collection

Routine data on surgical procedures and SSI will be collected via a standardized limited dataset per routine DICON practices (Table 4). No identifiable patient or surgeon data are transmitted to the DICON Surgical Database.

Table 4. Variables in the DICON Surgical database

All surgical patients	Hospital Type of procedure Patient identifier Date of procedure Age Sex Surgeon identifier Start/stop times ASA score Wound class Risk index SSI (Yes/No)
Infection	Date of infection Type of SSI Location at diagnosis Organism

When a signal is identified, data will be collected on the rationale for signal adjudication (action/no action). If a signal requires action, additional data will be collected on the recommended steps and findings.

Endpoints

Primary endpoint:

- Differences in the rates of SSI between clusters receiving intervention compared to clusters receiving traditional surveillance and feedback alone.
    a. SSI rate will be calculated as number of SSI/100 procedures
    b. SSIs will be defined using standard NHSN definitions
        i. DICON personnel train local infection preventionists about how to use and interpret SSI definitions. Thus, standard definitions and methods are used at all study hospitals.
    c. Cluster-level risk adjustment will be performed using median surgical volume[27] and median NHSN Risk Index (an operation- and patient-specific risk score that predicts SSI)[28,29] per cluster.

Secondary endpoints:

- Several secondary outcomes will be compared between clusters receiving intervention and clusters receiving traditional surveillance and feedback

    a. Proportion of SSIs determined to be potentially preventable
    b. Description of and difference in number and type of signals
    c. Difference in number of outbreaks identified
    d. Difference in number of investigations of increased rates of SSI
    e. Total number and differences in proportion of signals that led to investigations
    f. Time required to investigate signals
    g. Timing of signals

Exploratory endpoints

- None

Data Collection Strategy and Sources

The majority of data collection will occur through methods already developed and utilized by study hospitals. In brief, each hospital routinely submits limited datasets to the DICON Surgical Surveillance Database, including all data listed in Table 4. Data definitions and data collection

methods are standardized across DICON hospitals. Following signal adjudication, additional data will be collected in a REDCap database to document actions and rationale.

Blinding

SSI signals prospectively identified using optimized SPC methods during the intervention period will undergo blinded review to ensure that signal adjudication occurs without knowledge of which hospital cluster generated the signal. The study coordinator will unblind the signal, and, if the hospital cluster is randomized to intervention, the study team will proceed with the actions required to appropriately respond to the identified increase in SSI. If the hospital cluster is a control cluster, then the signal will be documented but no further action will be taken.

Data Monitoring

No formal interim analyses involving hypothesis testing is planned.

5.2 Other Study Procedures

We will not enroll patients as part of this protocol. Therefore, the following sections are not applicable:

1. Screening
2. Enrollment/baseline
3. Follow-up
4. Final study visit
5. Follow-up safety phone call
6. Early termination visit
7. Unscheduled visit
8. Laboratory evaluations

6 STUDY PRODUCT DESCRIPTION

Not applicable

6.1 Concomitant Medications/Treatments

Not applicable

7 ASSESSMENT OF SAFETY

We are not enrolling patients; therefore, the following sections are not applicable:

1. Specifications of safety parameters
2. Methods and timing for assessing, recording, and analyzing safety parameters
3. Guidelines for assessing intensity of an adverse event
4. Guidelines for determining causality
5. Discontinuation due to adverse events
6. Reporting procedures (for AE)
7. Type and duration of follow-up of participants after adverse events
8. Halting rules
9. Safety oversight

8 CLINICAL MONITORING

ICH E6 states that the purpose of monitoring is to ensure the rights of subjects, obtain accurate data, and conduct trial in accordance with protocol and applicable regulations. Routine procedures in our study group and through the research infrastructure at DUHS ensure the qualification of hospital personnel to conduct the trial, regulatory requirements (e.g. IRB review), protocol training, data quality monitoring procedures, hospital data completion expectations (e.g. completeness, frequency, etc.). Rights of subjects will be maintained at all times as outlined in the Privacy section.

9 STATISTICAL CONSIDERATIONS

9.1 Design and Sample Size Considerations

The study is designed as a multicenter, stepped wedge cluster randomized trial.

Power calculation. In our power calculation, we utilized 3 years of pilot data from 101 cluster in 29 DICON hospitals (including 1,622 SSIs following 154,554 procedures). Power was evaluated via a simulation study where for each cluster, log(SSI rate) was generated from a multivariate normal distribution with the following assumptions: 1) cluster-specific SSI rate for traditional surveillance phases calculated from the pilot data (average rate was 1.33%), 2) residual variance for log(SSI rate) of 0.76, 3) within-cluster correlation of 0.36, and 4) between cluster correlation of 0.39 in the same time step and 0.2 in different steps. Based on these assumptions, a study with 101 cluster in 29 DICON hospitals, 12 steps and an average of 127 procedures per cluster per 3-month step would have 90% power to detect a 25% decrease in the SSI rate between optimized SPC methods and traditional surveillance.

9.2 Planned Interim Analyses

There will be no planned interim analyses for safety in this protocol.

9.3 Participant Enrollment and Follow-Up

Individual subjects will not be enrolled. We will enroll 29 hospitals in the DICON network to participate in this quality improvement project. As long standing members of DICON, these hospitals will continue to participate in all routine network activities during and following the study.

9.4 Analysis Plan

9.4.1 Analysis

Data will be summarized using standard statistical methods.

Primary analyses

The primary outcome will be analyzed using a generalized estimating equations approach with a Poisson model or negative binomial model (if overdispersion is detected in the Poisson model), which will model SSI rate at a cluster level as a function of time (step) and intervention phase (traditional vs. optimized SPC feedback), while accounting for within-cluster correlation over time and between-cluster correlation within each study hospital. This model will utilize the data from all steps, including the baseline period. To account for any potential residual confounding, we will consider including cluster-level risk-adjustment variables in the model, as described in the previous section. Inference about the model parameter corresponding to the intervention phase will be used to address the main hypothesis (2.1). In case the number of zeroes per cluster exceed the number of zeroes modeled by Poisson (or negative binomial) distribution, we will consider a zero-inflated Poisson (negative binomial) model.

Secondary analyses

The outcome of superficial-incisional, deep-incisional, organ/space, and/or complex SSIs will be analyzed similarly to the primary outcome. The rate of signals per 100 procedures performed will be compared between optimized SPC and traditional surveillance methods using similar approach as for the primary outcome. Sensitivity and positive predictive value to identify important increases in SSI rates (defined as signals that lead to investigations) will be compared between optimized SPC and traditional surveillance methods using chi-square or Fisher's exact test, as appropriate. For a subset of true positive signals are generated by both methods, average time between

signals will be summarized, and proportion of true positive signals in which optimized SPC methods found the signal first will be estimated and compared to 50%. The remaining secondary outcomes will be analyzed using summary statistics only.

Full details of the statistical analysis will be specified in the statistical analysis plan prior to the study database lock.

Data Acquisition. See above

10 LIMITATIONS AND POTENTIAL SOLUTIONS

The study has potential limitations. With a SSI prevalence just over 1%, we have insufficient power to randomize at the hospital-level or to perform a truly “controlled” two-arm trial. Instead, we are using a stepped wedge version of the cross-over design and randomizing at the level of clusters within hospitals to achieve adequate power. We will account for potential longitudinal bias in the analysis by explicitly modeling time effect at each "step". We will conservatively impose only a general assumption of additivity on the time effect, without assuming its functional form (e.g. linear or quadratic) in time. Second, using clusters as the unit of randomization also may lead to bias. Local infection preventionists (IP) will interact with surgeons in all clusters within a hospital. Thus, it is possible that recommendations specific to one cluster (after a signal is reviewed) could be transmitted to all surgeons (and thus all clusters) within the hospital (including clusters not yet receiving the intervention). We will educate each DICON IP about limiting feedback derived from a signal to only the surgeons who perform procedures within the specific cluster. As currently designed, we do not expect surgeons within one cluster to perform procedures included in other clusters. Similarly, as most surgeons in DICON community hospitals are part of private practices specific to the type of surgery within the cluster, we foresee little risk of “contamination” between clusters. Finally, diagnosis has inherent delays, as SSIs are diagnosed, on average, 3 weeks after the procedures. In addition, IPs often wait to add SSI data to infection control databases based on work flow and effort available. We have discussed the importance of timely SSI data entry on SSI surveillance in general and this project. We will monitor the time between procedure and diagnosis during the study and provide feedback to hospitals that are outliers.

11 IMPLICATIONS

Completion of this SA will lead to the most detailed analysis of the use of SPC methods to prevent HAI to date. We expect that the optimized SPC method will be more effective at identifying and preventing SSIs than traditional surveillance and feedback methods. As such, this work will potentially change the way US hospitals perform surveillance and provide feedback for SSI. To this end, we will discuss our findings with colleagues in the CDC to determine if our methods can be integrated into standard NHSN surveillance techniques. We expect to publish multiple manuscripts outlining the theoretical and actual benefit of SPC methods for preventing SSI. Finally, results from this trial will be directly informative for future studies using SPC methods to identify changes in other HAIs and process measures.

12 PARTICIPANT CONFIDENTIALITY

We will not enroll patients as part of this project. Per standard procedures, limited datasets will be sent the DICON Surgical Surveillance Database. No patient or surgeon-specific information will be available in these files.

13 INFORMED CONSENT PROCESS

We will not enroll patients. As this study is based on quality improvement (QI) strategies we will seek IRB exemption and, if necessary, waiver of informed consent.

14 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

No source documents will be used by this protocol.

15 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will ensure that all study personnel are appropriately trained and applicable documentations are maintained.

16 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

16.1 Institutional Review Board

The investigator will ensure that the protocol is reviewed and approved by the DUHS IRB prior to the start of any study activities. The IRB will be appropriately constituted and will perform its functions in accordance with US regulations, ICH Good Clinical Practice guidelines, and local requirements as applicable.

16.2 Informed Consent

We will not enroll patients. As this study is based on quality improvement (QI) strategies, we will seek waiver of informed consent.

16.3 Data Confidentiality

This is a minimal risk study. Data will be stored on encrypted Duke Medicine servers (all surgical data collated in the DICON Surgical Database) and/or in our REDCap database (all other data collected for the study).

16.4 Study Discontinuation

This study may be terminated at any time by the principal investigator (PI) in consultation with the AHRQ.

17 DATA HANDLING AND RECORD KEEPING

17.1 Data Management Responsibilities

DICON IT personnel will be responsible for data management required for the DICON Surgical Database, per routine DICON practices. The study coordinator will be responsible for documentation required for the study.

Data Capture Methods

REDCap is a toolset and workflow methodology for electronic collection and management of research and clinical trial data. Both REDCap and REDCap Survey systems provide secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails and reporting for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

The REDCap program will serve as the portal for data entry by the study coordinator. Data entered into this database will be password protected and only accessible by study personnel. All access to this secure separate database will be monitored and logged.

Specific Data Management. Surgical data, including SSI data, will be maintained in the DICON Surgical database. Data related to signal adjudication and reaction will be entered into REDCap databases.

17.2 Study Data Retention

Research records and data will be kept for a minimum of 6 years after final reporting or publication.

17.3 Protocol Deviations

Deviations from the study protocol (e.g., randomization scheme) will be documented.

18 PUBLICATION POLICY

Following completion of the study, the investigator will publish the results of this research in a scientific journal.

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20 APPENDIX 1. STUDY HOSPITALS

Hospital Name	Location	Letter of Support Received
Augusta Health	Fishersville, VA	yes
Central Carolina Hospital	Sanford, NC	yes
Chesapeake Regional Healthcare	Chesapeake, VA	yes
Columbus Regional Healthcare	Whiteville, NC	yes
Conway Medical Center	Conway, SC	yes
Danville Regional Medical Center	Danville, VA	yes
Duke Raleigh Hospital	Raleigh, NC	yes
Duke Regional Hospital	Durham, NC	yes
Frye Regional Medical Center	Hickory, NC	yes
Granville Medical Center	Oxford, NC	yes
Harnett Health	Dunn, NC	yes
High Point Regional	High Point, NC	yes
Indian River Medical Center	Vero Beach, FL	yes
Iredell Health System	Statesville, NC	yes
Maria Parham Medical Center	Henderson, NC	yes
Morehead Memorial Hospital	Eden, NC	yes
Nash Healthcare System	Rocky Mount, NC	yes
New Hanover Regional Medical Center	Wilmington, NC	yes
Person Memorial Hospital	Roxboro, NC	yes
Piedmont Atlanta	Atlanta, Ga	yes
Piedmont Henry Hospital	Stockbridge, GA	yes
Piedmont Fayette Hospital	Fayetteville, GA	yes
Piedmont Newnan Hospital	Newnan, GA	yes
Rex Healthcare	Raleigh, NC	yes
Scotland Healthcare	Laurinburg, NC	yes
Southeastern Regional Medical Center	Lumberton, NC	yes
Twin County Regional	Galax, VA	yes
Wayne Memorial	Goldsboro, NC	yes
Wilson Medical Center	Wilson, NC	yes