A Cluster Randomized Controlled Trial Comparing the Safety Action Feedback and Engagement (SAFE) Loop with an Established Incident Reporting System

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5/6/2021	Clarified that all surveys and interviews of nurses will occur during nursing hours. (p.10) Changed incentive for interviews from gift cards to a lottery for an iPad (p. 10, 20). Added details on dissemination of intervention and recruitment procedures (p. 10, 11).	The intervention itself is considered a part of usual quality improvement activities. Change req by HR because gift cards are wages but a lottery for an iPad is not. Ensure recruitment of nurses working evenings and weekends.
10/15/2021	Revised to add information about the Advisory Board in section 10.1.5.	
3/22/2022	Implemented changes to hopefully increase response rate of nursing surveys: 1) study team will attend huddles and other meetings as feasible, 2) recruitment emails will be sent from the nursing director, 3) snacks will be provided regardless of participation, (section 5.5).	Response rates have been very low so far. These changes are to hopefully increase the response rate by increasing awareness of the survey and its importance.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Agency for Healthcare Research and Quality Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

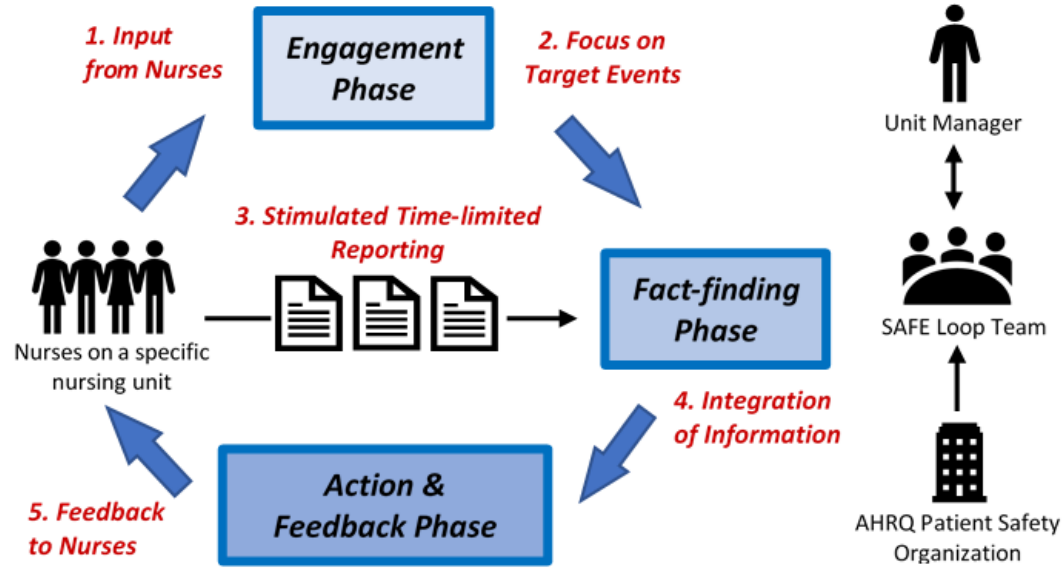
Title:	A Cluster Randomized Controlled Trial Comparing the Safety Action Feedback and Engagement (SAFE) Loop with an Established Incident Reporting System
Study Description:	This cluster RCT will test whether a novel intervention, the Safety Action Feedback and Engagement (SAFE) Loop, enhances incident reporting practices, improves nurses' perceptions of incident reporting, and lowers rates of high-priority medication events, as compared with using an existing incident reporting system.
Objectives:	This project seeks to transform hospitals' existing voluntary incident reporting systems into effective tools for improving patient safety. In this cluster RCT, we propose to test whether, compared with using an existing incident reporting system, implementing the SAFE Loop in acute care nursing units: • *Aim 1:* improves incident reporting practices by increasing the rate at which nurses report high-priority medication incidents (H1.1) and the number of contributing factors described per report (H1.2). • *Aim 2:* improves nurses' attitudes toward incident reporting, including perceptions of feedback and communication about error (H2.1) and of the frequency with which events are reported (H2.2). • *Aim 3:* reduces rates of high-priority medication events (H3.1) and high-priority medication events involving harm (H3.2).

Endpoints:	1) Incident reporting practices (rates at which nurses report high-priority medication incidents and numbers of contributing factors described per report). 2) Nurses' attitudes toward incident reporting using the AHRQ Hospital Survey on Patient Safety Culture™ (SOPS), particularly perceptions of feedback and communication about error and of the frequency with which events are reported. 3) Rates of high-priority medication events (determined via Institute for Healthcare Improvement Trigger Tool method of medical record review). Qualitative evaluation of implementation as per opinions of nurses.
Study Population:	A) *Nurses*: All 1,980 nurses on the nursing units will be eligible to participate in the SAFE Loop as well as Aims 1 and 3. Nurses will be eligible for participating in the survey (Aim 2) if they worked >50% time on one study nursing unit during a 6-month study period. Nursing unit managers and nurses in the study units will also be eligible to participate in semi-structured interviews to help characterize the implementation of SAFE Loop (32 participants). B) *Patients*: Cedars-Sinai has 49,000 inpatient, 7,700 observation, and 58,000 emergency department encounters in a typical year, resulting in a total of 294,470 patient-days of care in study nursing units per year. Under Aim 1, incident reports for about 1,663 patients will be analyzed. Under Aim 3, medical records for 1,520 eligible hospitalizations during the SAFE Loop study period will be randomly sampled and analyzed.
Description of Sites/Facilities Enrolling Participants:	20 Cedars-Sinai acute care nursing units in the main Medical Center
Description of Study Intervention:	We will conduct a cluster RCT to compare nursing units that implement the SAFE Loop, a system-level change in incident reporting, with nursing units that continue to use the existing reporting system. The Safety Action Feedback and Engagement (SAFE) Loop has three phases: Engagement, Fact-finding, and Action & Feedback. Across the three phases, the SAFE Loop has five Key Attributes: (1) obtaining input from nurses on which problems to address; (2) focusing on selected high-priority events, (3) prompting nurses to report the high-priority events for a designated period and write more informative reports; (4) following standardized investigative procedures to integrate information from sources internal and external to CSMC, and (5) providing feedback to nurses about safety problems and mitigation plans. During all phases, the SAFE Loop Team collaborates with frontline nurses and Unit Managers. (See schemata in Section 1.2)
Study Duration:	60 months
Participant Duration:	24 weeks

1.2 SCHEMA

Figure 1: Existing Voluntary Incident Reporting Systems (Control Arm)

Figure: SAFE Loop Reporting System (intervention arm, which is added to conditions in control arm)



1.3 SCHEDULE OF ACTIVITIES (SOA)

Timeline depicting individual nursing unit involvement in 3 phases and 5 attributes of SAFE Loop

Week→	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	…	24
1. Engagement																					
Obtain input	■	■	■																		
Select Target Event				■																	
2. Fact-finding																					
Train nurses					■	■															
Stimulate reporting					■	■	■	■	■	■	■	■	■	■	■	■				…	
Analyze & investigate							■	■	■	■	■	■	■	■	■	■				…	
Integrate information					■	■	■	■	■	■	■	■	■	■	■	■				…	
3. Action, Feedback																					
Develop plan									■	■	■	■	■	■	■	■	■	■	■		
Distribute feedback																			■		
Implement, sustain																			■	■	■

Timeline depicting study activities over the entire 5-year study period, including milestones

♦ Milestone

Year →	1				2				3				4				5			
Quarter Year →	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Clinical Events																				
Randomize nursing units				■																
Study Periods																				
--Baseline periods			■	■			■	■												
--Implementation/control periods					■	■			■	■										
--Follow-on periods (Aim 3)							■	■			■	■								
Trial Preparation & Oversight																				
Prepare DSM Plan, Protocol		■	■	♦																
Prepare & submit IRB application	■	■		■																
Advisory board meetings		■		■											■					
Develop SAFE Loop training materials	■	■	♦																	
Monitoring trial & potential effects					■	■	■	■	■	■										
DSM oversight assessments			■				♦				■					♦				
Data Collection																				
Incident reports (Aim 1, retrospective)																				
--Refine & test scoring tools	■	♦																		
--Train abstractors				■																
--Evaluate incident reports							■	■	■	■	■	■	♦							
Surveys (Aim 2, prospective)																				
--Develop & test survey interface		■	♦																	
--Survey clinicians & staff				■		■		■		♦										
Med events (Aim 3, retrospective)																				
--Develop chart review screening tools	■	■	■	♦																
--Develop event scoring tools				♦																
--Train nurse abstractors				■																
--Screen for possible med events				■	■	■	■	■	■	♦										
--Train physician reviewers							■	■												
--Confirm, classify medication events								■	■	■	■	■	■	♦						
Qualitative Analysis of Implementation																				
--Develop interview guides				■	■	♦														
--Conduct interviews							■				♦									
--Code and analyze interviews								■	■	■	■	■	♦							
Analysis																				
Data cleaning											■	■	■	■	■					
Descriptive analyses												■	■	■	■	■	■			
Analyses of primary outcomes												■	■	■	■	♦				
Secondary analyses													■	■	■	■	■	■		
Dissemination																				
Manuscripts, conferences																■	■	■	■	■
Media campaign																		■	■	■
Dissemination together with ISMP																			■	■

2 INTRODUCTION

2.1 STUDY RATIONALE

This project seeks to transform hospitals' existing voluntary incident reporting systems into effective tools for improving patient safety.

Substantial progress has been made in some areas of patient safety, but medication errors and other problems continue to harm many thousands of patients each year. In other high-risk industries, voluntary incident reporting is widely used to improve safety. Incident reporting is also widely used in hospitals, but the reporting systems do not function optimally. Nurses file most reports, but they experience multiple barriers to reporting, including uncertainty about what to report, lack of feedback, and doubt about how hospitals will use the reports. Nurses submit thousands of reports each year, but the reported incidents represent a lower-risk subset of medical errors, the reports impart few actionable insights, and no standardized procedures exist for conducting follow-up investigations.

The Safety Action Feedback and Engagement (SAFE) Loop has five key attributes designed to transform hospital incident reporting systems into effective tools for improving patient safety: obtaining nurses' input about which medication safety problems to address; focusing on selected high-priority events; prompting nurses to report high-priority events during a designated period and training them to write more informative reports; integrating information from reports, investigations, and other internal and external sources; and providing feedback to nurses on the problems identified and mitigation plans.

If effective, the SAFE Loop will have several benefits: increasing nurses' engagement with reporting, producing more informative reports, enabling safety leaders to understand problems and design system-based solutions more effectively and more efficiently, and lowering rates of medication errors. In turn, receiving feedback about problems and system-based solutions will further improve nurses' perceptions of reporting. In addition to the local benefits to hospitals that implement the SAFE Loop, these changes will create secondary benefits nationally by enhancing the functioning of AHRQ Patient Safety Organizations, which rely on incident reports as critical sources of insights into safety concerns in hospitals and potential solutions.

2.2 BACKGROUND

Despite decades of effort by policymakers, hospitals, and clinicians**, medical errors still contribute to numerous patient deaths and injuries in U.S. hospitals each year**. In other high-risk industries, such as aviation, voluntary incident reporting is a widely used and effective technique through which frontline personnel describe events—particularly near misses—that serve as early warnings of safety problems. Personnel who witnessed the incidents write narrative descriptions that reveal critical details including contributing system and human factors, then organizations analyze the narratives, conduct follow-up investigations, and ultimately modify systems to reduce the likelihood of future harm.[1,2]

Incident reporting systems have existed in U.S. hospitals for over 50 years, but they have not been as effective at improving patient safety, for three basic reasons. First, although nurses file most reports and believe reporting is a professional responsibility, they experience barriers to reporting including uncertainty about which events to report and lack of feedback about how reports are used. Nurses describe hospital reporting systems as a "black hole." Second, hospitals receive thousands of reports each year, but most reports address low-risk problems and provide little information on contributing

factors. Third, how hospitals follow-up on incident reports varies and no optimal procedures for following up have been described.

Despite Years of Effort, Medical Errors Still Harm Thousands of Hospitalized Patients Each Year. Progress has occurred in important areas such as healthcare-associated infection, but improvements in other areas have been modest.[10,11] A 2010 study revealed that the rate of harms due to medical care remained constant at 25% of hospitalizations over a 5-year period.[12] The same year, 13.5% of Medicare beneficiaries were found to experience adverse events during hospitalization.[13] A 2019 study of death certificates found that adverse effects of medical treatment increased from 1990 to 2016 due to the aging population.[14]

Voluntary Incident Reporting Has Been an Effective Strategy for Improving Safety in Other High-risk Industries. *Voluntary incident reporting* is a technique through which frontline personnel describe events that posed risks to safety, particularly incidents that were intercepted or happened not to cause harm. A fundamental tenet of effective reporting is that first-hand witnesses write *narrative descriptions* that reveal *contributing factors* (the specific conditions leading up and potentially causing each event), sharing insights that might otherwise be rapidly forgotten. By analyzing the narratives and conducting follow-up investigations, organizations learn how *system factors* (facilities, equipment, tasks, personnel availability and qualifications, and organizational culture and goals) contributed to incidents, either directly or by influencing human performance (*human factors,* including errors, mistakes, and violations). These insights enable organizations to modify systems to reduce the likelihood of future harm.[1,2]

Voluntary incident reporting has a long history and is widely used in the aviation, maritime, chemical, nuclear, and railway industries. Research in these settings has demonstrated that a major accident is usually preceded by many weak signals, called *near misses* (errors that might have led to an adverse event but that were intercepted or happened not to cause harm).[15] Studies in the oil, food, construction, health and transport sectors in the U.K. revealed that, for each major event, there are 7 minor events and 189 near misses.[16] Furthermore, studies in the aviation and chemical industries showed that near misses and harmful incidents share the same causes.[17] Thus, reporting near misses expands opportunities to avoid future harmful incidents.

Incident Reporting Systems Already Exist in Most U.S. Hospitals. Whereas safety has been the sole purpose in other industries, reporting has served dual objectives in U.S. hospitals since 1965: (1) alerting risk managers when a specific event could lead to litigation and (2) preventing problems that are common sources of malpractice claims.[18] Hospitals rely on nurses to file most reports.[3] How hospitals handle the reports varies: reports may be transmitted to the manager of the nursing unit, safety leaders, and/or risk managers. Reports can trigger investigations locally or systemwide. Sometimes reports are used to discipline the individuals involved. Nurses describe what happens after reporting as a "black hole" because they seldom learn how reports were used (**Figure 1**).[7,19-21]

Hospital Reporting Systems Are Not Employed Effectively. To share insights about patient safety issues and opportunities for improvement, AHRQ created *Patient Safety Organizations (PSOs)* with the unique ability to aggregate incident reports from multiple health systems.[22] However, aggregating data requires effective reporting systems within hospitals and current systems within hospitals function poorly.[19,20]

Three types of problems limit the effectiveness of hospital reporting systems. *1. Nurses and other staff experience barriers to reporting, particularly lack of engagement and feedback*. While nurses believe that incident reporting is a professional obligation, they are often uncertain about what to report and

what information to include. Nurses fear triggering punitive responses and doubt whether any responsive actions will be taken to improve systems of care.[19,23,24] Indeed, lack of feedback is the primary deterrent to reporting.[24] In over 2000 hospitals, only 13 reporting systems provided any feedback to personnel who filed reports.[25] The dearth of feedback not only contributes to a sense that reports go into a "black hole," it undervalues the importance of nurses in designing and implementing solutions. When feedback is provided, it is a powerful facilitator of reporting.[24] *2. The reports currently received are often of limited usefulness to improving safety*. Although underreporting is pervasive, hospitals typically receive thousands of reports per year.[26,27] Research by **Nuckols** found that many reports describe similar events and address lower-risk problems like infiltrated peripheral intravenous (IV) catheters or missed doses of medication.[3] Higher-risk incidents are underreported.[3] Simply increasing the quantity of reports, as opposed to the priority of the reported events, may degrade the signal-to-noise ratio, obscuring the ability to identify critical events. Additionally, studies by **Nuckols** and **Cohen** (Co-I) showed that only 32-65% of reports contain any information on contributing system factors.[4,8,9] If incident reports do not capture high-priority events or reveal helpful insights, safety leaders may learn too little to act on the information in reports. *3. Optimal procedures for following up on incident reports in hospitals have not been described.* Hospitals have over-emphasized the collection and rudimentary analysis of large volumes of reports, unlike in aviation, where systematic investigation and prompt action are the goals.[28,29]

Specific Changes Would Transform Hospital Reporting Systems into Effective Tools for Improving Safety. Engagement is needed between nurses and safety leaders throughout the process of reporting, investigation, and improvement. Events that are common, preventable, and potentially severe should be the highest priority. The systems should emphasize near misses, to reduce the chance that reporters might be blamed. Reports should provide rich detail on contributing factors, facilitating follow-up investigations. Lastly, reporting systems should provide feedback about the problems identified and mitigation plans.[1]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There are two categories of study subjects who will be affected by SAFE Loop:

1. **Nurses** and nursing unit managers who work in the nursing units, and
2. **Patients** who receive care there.

Table of Study Procedures and Associated Risks for Each Group.

Study Procedure	Risks for Nurses	Risks for Patients
1. Organizational Quality Improvement Intervention: Implementation of SAFE Loop in nursing units	Psychological distress or loss of professional reputation may occur if a nurse is blamed for a medication error after an incident report is submitted. Risks are similar to those in usual nursing practice because nurses already submit incident reports.	Medication error. Risks are unlikely but may occur if the nursing units inadvertently implement changes that worsen rather than improve medication safety, as intended.

	To further mitigate the risks, we will train nurses to emphasize reporting of near misses and no-harm events (which are less likely to result in punitive responses by unit managers) and train unit managers in the "just culture" approach, which emphasizes changing systems of care rather than blaming individual nurses when medication errors occur.	
2a. Research data collection: nursing work schedules, to assess nurse eligibility for survey	Inadvertent disclosure of individually identifiable information on nursing work schedules. This data source does not include sensitive information.	Not applicable.
2b. Research data collection: surveys of nurses on attitudes toward reporting and patient safety culture	Inadvertent disclosure of individually identifiable information on nursing survey. Survey does not involve sensitive information and it is already routinely deployed in this hospital.	Not applicable.
3. Research data collection: analysis of incident reports to assess rate and quality of reports	Inadvertent disclosure of individually identifiable information. This data source includes sensitive information such as errors that nurses may have committed. Data to be extracted will not include individually identifiable information about nurses.	Inadvertent disclosure of protected health information (PHI). Incident reports contain patient identifiers and PHI. Data to be extracted will not contain patient identifiers aside from randomly assigned study identification numbers to facilitate linkage to other datasets.
4. Research data collection: analysis of medical records to identify medication events	Not applicable. Data to be extracted will not include individually identifiable information.	Inadvertent disclosure of PHI. Medical records contain patient identifiers and PHI. Data to be extracted will not contain patient identifiers aside from randomly assigned study identification numbers to facilitate linkage to other datasets.
5. Research data collection: interviews with nurses who	Inadvertent disclosure of individually identifiable information. The interviews will not include sensitive information.	Not applicable.

implemented the intervention		
6. Research data collection: Extraction of electronic health record variables	Not applicable.	Inadvertent disclosure of PHI. Data to be extracted will not contain patient identifiers aside from randomly assigned study ID numbers to facilitate linkage to other datasets.

2.3.2 KNOWN POTENTIAL BENEFITS

Nurse participants: Nurses may benefit from the SAFE Loop intervention through improvements in their skill in reporting medication errors; such reporting is considered a basic responsibility in nursing practice. Additionally, participation may enhance professional satisfaction, because the nurses on each study unit come together to choose a medication safety problem to solve and then help to collect useful information on that problem by filing incident reports. The intervention is also designed to improve the reporting culture at the institution, shifting from a culture that may blame reporters for events to a culture that uses reports as tools for improving systems of care.

Patient participants: Patients may benefit from the SAFE Loop intervention through reductions in rates of medication errors. Additionally, improved incident reporting systems may help to lower the rates of harmful medication errors at the study hospital.

Society: If effective, the research will demonstrate a strategy for improving patient safety in hospitals through the use of incident reporting. In the future, hospitals that implement the SAFE Loop may experience several benefits: increasing nurses' engagement with reporting, collecting more informative reports, enabling safety leaders to understand problems and design system-based solutions more effectively and more efficiently, and lowering rates of medication errors. In turn, receiving feedback about problems and system-based solutions will further improve nurses' perceptions of reporting. In addition to the local benefits to hospitals, these changes will create secondary benefits nationally by enhancing the functioning of AHRQ Patient Safety Organizations, which rely on incident reports as critical sources of insights into safety concerns in hospitals and potential solutions.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks of nurse and patient participation are *no greater than they normally encounter during the course of clinical care in the hospital setting*, while the potential benefits to participants and society are substantial due to possible reduction in harmful adverse events. Thus, on balance, the risks of participation are counterbalanced by the potential for substantial benefits to participants and society.

3 OBJECTIVES AND ENDPOINTS

In this cluster RCT, **we propose to test whether**, compared with using an existing incident reporting system, **implementing the SAFE Loop in acute care nursing units:**

Aim 1*:* improves incident reporting practices by increasing the rate at which nurses report high-priority medication incidents (H1.1) and the number of contributing factors described per report (H1.2).

Aim 2: improves nurses' attitudes toward incident reporting, including perceptions of feedback and communication about error (H2.1) and of the frequency with which events are reported (H2.2).

Aim 3: reduces rates of high-priority medication events (H3.1) and high-priority medication events involving harm (H3.2).

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1: To determine whether SAFE Loop implementation increases the number of contributing factors described per report (H1.2)	(H1.2) The number of system plus human contributing factors per incident report	Reports including more contributing factors will allow quality improvement personnel to develop solutions that are better-informed
Aim 2: To determine whether SAFE Loop implementation improves nurses' attitudes toward incident reporting, including perceptions of feedback and communication about error (H2.1)	(H2.1) Hospital Survey on Safety (SOPS) Culture Survey performance on composite measure on "Feedback & Communication About Error"	Nurses involved in SAFE Loop will confirm that an effective safety action loop has been established by scoring higher on measures of feedback/communication about error
Aim 3: To determine whether SAFE Loop implementation reduces rates of high-priority medication events (H3.1)	(H3.1) Rate per 1,000 patient-days of Target Medication Events selected by nursing units in intervention groups	Nursing units involved in the intervention arms will reduce the number of target medication events compared to control group units
Secondary		
Aim 1: To determine whether SAFE Loop implementation increases the rate at which nurses report high-priority medication incidents (H1.1) and the number of contributing factors described per report	(H1.1) The rate per 1000 patient-days of incident reports addressing one of the Target Medication Events The number and type of patient factors (e.g. language barrier) associated with incident reports	If nurses report more important events per patient-day, quality improvement personnel will have more opportunities to develop targeted improvement solutions Patient factors may lead to an increased risk of adverse drug events
Aim 2: To determine whether SAFE Loop implementation improves nurses' attitudes toward incident reporting, including perceptions of the frequency with which events are reported.	(H2.2) SOPS Culture Survey performance on composite measure on "Frequency of Events Reported"	Nurses will demonstrate greater engagement in SAFE Loop by scoring higher on measures of frequency of events reported
Aim 3: To determine whether SAFE Loop implementation reduces rates of high-priority medication events involving harm	Rate of events involving harm	The most severe events are the highest priority for prevention.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
Qualitative analysis of implementation:	Qualitative reports from nurses about the process of implementation	If the SAFE Loop improves outcomes, understanding how it worked will enable the intervention to be adapted for use at other hospitals.

4 STUDY DESIGN

4.1 OVERALL DESIGN

We plan to conduct a single-site cluster RCT of 20 acute care nursing units in the main Medical Center to compare use of the SAFE Loop (intervention nursing units) and an existing incident reporting system (control nursing units). Implementation of the intervention will be sequential in two phases (5 intervention and 5 control units will be randomized at a time). Randomization will occur in blocks to assure the similarities of the nursing units, with 4 nursing units per block, matched on patient population, size of the nursing unit, and other factors.

Corresponding to three study Aims above, outcome measures include:

- (Aim 1) incident reporting practices (rates at which nurses report high-priority medication incidents and numbers of contributing factors described per report),
- (Aim 2) nurses' attitudes toward incident reporting (AHRQ Hospital Survey on Patient Safety Culture™, particularly perceptions of feedback and communication about error and of the frequency with which events are reported), and
- (Aim 3) rates of high-priority medication events (determined via IHI Trigger Tool method of medical record review).

Analyses will compare changes in outcomes between from before to after implementation in intervention and control arms. Qualitative interviews of nurses the SAFE Loop intervention arm will provide insight into implementation.

To minimize bias while also facilitating study feasibility, randomization will be done at the nursing unit level, and research staff involved in data collection will not have access to information on which nurses and patients were assigned to which arm. Also to minimize bias, nurses participating in the survey in Aim 2 will be informed that the results will be analyzed as part of a study on patient safety and incident reporting, without specifically linking the survey to the SAFE Loop study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A cluster RCT is an appropriate balance the rigors of a randomized control trial against the practical considerations of implementing a study across multiple nursing units of a large medical center. The design will enable the research team to adequately engage and train participants in nursing units while also using control nursing units to measure the effectiveness of the SAFE Loop intervention.

4.3 JUSTIFICATION FOR DOSE

Not Applicable

4.4 END OF STUDY DEFINITION

A nurse or nursing unit will be considered to have completed the study upon finishing all phases of the study including the last procedure shown in Section 1.3. The end of the study is defined as completion of last procedure shown in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Study Nursing Units:

The study will include 34 acute care areas within Cedars-Sinai medical Center, which are grouped together into 20 nursing units by virtue of sharing the same nursing unit manager (**Table**). To facilitate blocked randomization, we grouped similar nursing units together into 5 blocks with four nursing units per block. The four nursing units within each block are as similar as possible (e.g., medical units are grouped together, ICUs are grouped together, etc.).

Table: Study Nursing Units, Patient Populations, Type, Size, & Allocation to Blocks

	Unit Areas	Typical Patient Population	Type	Nurses	Pt-Days*
Block 1: Larger medical floor units					
A	4SE, 4SW	Adult oncology	Floor	118	22,322
B	5NE, 5NW	Cardiology	Floor	116	21,534
C	5SE, 5SW	Adult medicine, gastroenterology	Floor	103	22,025
D	7SE, 7SW	Adult medicine	Floor	92	22,025
Block 2: Smaller medical floor units and emergency department					
A	6SE, 6SW	Congestive heart failure	Floor	104	18,552
B	ED	Emergency department (ED)	ED	167	19,108
C	3-SCCT	Medicine, congestive heart failure	Floor	50	10,188
D	3NW	Short stay medical	Floor	41	2,437
Block 3: Surgical floor units					
A	6NE, 6NW 6ICU	Kidney & liver transplant, cardiac surgery, Post cardiac-catheterization recovery	Floor, ICU	122	21,493
B	7NE, 7NW	Med/surg orthopedics	Floor	106	20,901
C	8SE, 8SW	Med/Surg bariatrics, GI surgery	Floor	100	15,230
D	8NE, 8NW	Neurosurgery, Med/surg spine	Floor	78	15,230
Block 4: Adult intensive care units					
A	4N-SCCT, 6-SCCT	Cardiac ICU, Cardiothoracic surgery ICU	ICU	130	10,711
B	5-SCCT	Surgical and trauma ICU	ICU	91	6,381
C	7-SCCT	Respiratory/medical ICU	ICU	69	7,085
D	8-SCCT, 4NW	Neurosurgical ICU, Adult stroke/medicine	ICU, Floor	124	17,424
Block 5.1: Obstetric and postpartum units					
A	3NE	Maternal-fetal care (obstetrics)	Floor	123	14,486
B	3SE, 3SW	Post-partum	Floor	115	13,476
Block 5.2: Pediatric units					
C	4S-SCCT, 4NE	Pediatric and congenital cardiac ICU, Pediatrics	ICU, Floor	44	3,903
D	4NICU	Neonatal ICU	ICU	87	9,959
*Patient-days of care on nursing unit per year.			**Total**	1980	294,470

***Nurses*:**

- Aims 1 & 3 (SAFE Loop Incident Reports and Medical Record Review): All 1,980 nurses on the nursing units will be eligible to participate in the SAFE Loop and therefore participate in Aims 1 and 3.

- Aim 2 (Survey): Nurses will be eligible for survey administration if they worked >50% time on one study nursing unit during a 6-month study period; this will ensure adequate exposure to the study conditions and the opportunity to complete baseline and follow-up surveys. About 1,980 nurses will be eligible.
- Qualitative analysis of implementation: Nurse unit managers and nurses will be eligible for the qualitative interview if they worked at least 50% time on the study nursing units for the entire duration of a SAFE Loop implementation period. (We will enroll 32 participants out of a pool of approximately 800 eligible nurses.)

***Patients*:**

Cedars-Sinai has a total of 294,470 patient-days of care in eligible nursing units per year. Patients located in experimental and control group nursing units will be eligible for participation. If patients transfer between nursing units during the study, analyses will allocate each day of the hospitalization to the unit where the patient was that day. For the review of medical records under Aim 3, we will randomly select 1,520 patients hospitalized during the baseline and follow-on periods.

5.2 EXCLUSION CRITERIA

We will exclude outpatient clinics, operating/ procedure rooms, post-anesthesia care, and diagnostic and therapeutic services.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Not applicable

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment is not applicable to participation in the SAFE Loop because the intervention is implemented at the level of the nursing unit. This is true for both nurses and patients on the study nursing units.

Outcome Assessment

Nurses

- Aim 2 (AHRQ Hospital Survey on Patient Safety Culture): To identify nurses eligible for the survey, hospital administrators will access internal staffing databases listing the nurses who work on each of the nursing units, including names, email addresses, title/position, percent effort overall, dates of work on the study units (to identify nurses who joined or left during a study wave), and work schedule (to determine which nurses worked >50% on each unit). For the survey procedures, the response rate is relevant rather than the recruitment rate. During routine deployments at Cedars-Sinai of the AHRQ Hospital Survey on Patient Safety Culture, response rates on study nursing units have been 60% or higher on average. To optimize response rates, leaders on the study team will visit nursing units during the huddles and during other meetings on the nursing units shortly before and during each survey deployment. To reinforce completion of the survey and we will ask the nursing unit directors to send

eligible nurses an email notice expressing support for the research project and survey, explaining that completing the survey is voluntary, and letting the nurses know to expect the survey. The survey itself will be delivered electronically, via REDCAP using a weblink embedded in an email. During each deployment, we will deliver the survey up to four times to optimize response rates. We will also place fliers approved by the IRB on tack boards in common areas like break rooms and conference rooms away from public areas. We will incentivize completion of the survey at both the individual level and the nursing unit level. Nurses will be asked to complete the survey during working hours. Individual nurses will be entered into a lottery to win an iPad. When visiting the nursing huddles/meetings to prompt completion of the survey, study team members will bring gift baskets of healthy beverages and snacks. Study subjects will include women and minority groups, and will be diverse in terms of race and ethnicity. Because study subjects are nurses and nurses are more likely to be female, a majority of subjects will be female. We will neither conduct outreach for nor exclude any individuals on the basis of sex/gender, race, or ethnicity.

- Qualitative analysis of implementation: We will recruit 22 frontline nurses and 10 nurse managers to participate in a 30-minute qualitative interview post SAFE Loop implementation by visiting nursing huddles that are convened daily as part of routine organizational activities on the unit. We will also post fliers approved by the Marketing Dept in nursing break rooms and conference rooms away from public areas. Nurses will be entered into a lottery for an iPad for their participation. The recruitment rate is not applicable to participation in the SAFE Loop because we will continue to recruit nurses to participate in the qualitative interviews until we have completed 32. Study subjects will include women and minority groups, and will be diverse in terms of race and ethnicity. Because study subjects are nurses and nurses are more likely to be female, a majority of subjects will be female. We will neither conduct outreach for nor exclude any individuals on the basis of sex/gender, race, or ethnicity. Nurses will be asked to complete the interviews during working hours.

Patients

- Aim 1 (SAFE Loop Incident Reports): Not applicable; data are collected retrospectively.
- Aim 3 (Medical record and other record review to identify medication errors): Not applicable; data are collected retrospectively.

6 STUDY INTERVENTION

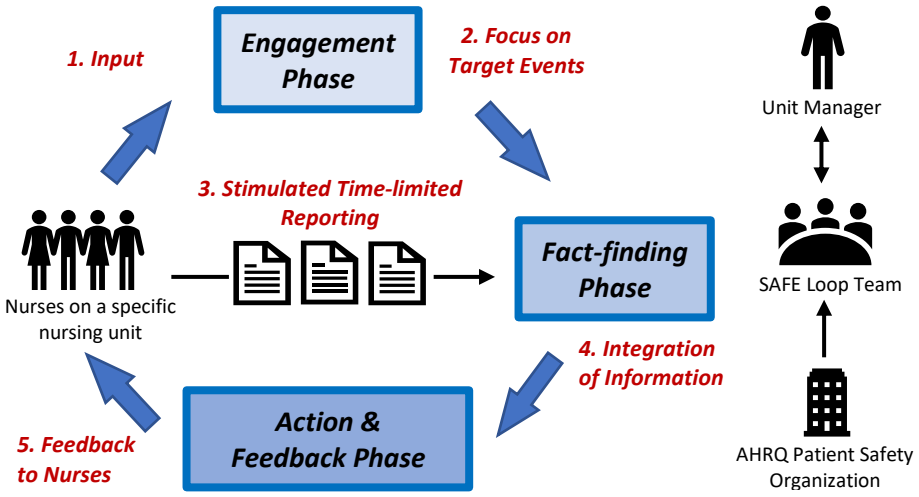
6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The SAFE Loop has **three phases: Engagement, Fact-finding, and Action & Feedback.** Across the three phases, the SAFE Loop has **five Key Attributes**. During all phases, the SAFE Loop Team collaborates with frontline nurses and Unit Managers. During the Fact-finding Phase, the team obtains and integrates information from an AHRQ Patient Safety Organization.

Although the SAFE Loop could apply to any problem, we will focus on medication errors because they are common,[34-37] occur on diverse nursing units, and can be evaluated using well-established methods. Also, nurses file most incident reports and are uniquely able to detect problems not only during drug administration but also during the ordering, dispensing, and monitoring stages in drug therapy.[38]

Five Key Attributes Designed to Maximize the Effectiveness of Reporting:



(1) Input from Nurses (Engagement Phase): Nurses are more likely to report events and adopt innovations addressing safety problems that they find to be particularly common, severe, or preventable.[39-41] The SAFE Loop Team, therefore, solicits input from nurses and Unit Managers on which problems to select and solve.

(2) Focus on Selected Target Event (Engagement Phase): To make the best use of investigative resources and obtain enough reports to understand each safety problem, the SAFE Loop focuses on *Target Medication Events* (errors and adverse events related to a selected, defined problem). These events will involve a particular clinical situation, drug class (e.g., opioids), population (e.g., kidney disease), type of error (e.g., duplicate therapy), and/or system factor (e.g., different protocols in ICU and floor units). Examples include: (1) nurses having challenges reconciling medications after patients go to the operating room, (2) pharmacists dispensing mislabeled medication, and (3) physicians ordering multiple sedating medications concurrently.

(3) Stimulated Time-limited Reporting (Fact-finding Phase): Lack of guidance about what and how to report deters reporting and limits reports' usefulness. The SAFE Loop Team prompts nurses to report many Target Medication Events during a certain period and teaches nurses to write more informative reports.

(4) Integration of Information (Fact-finding Phase): Because most safety problems are not unique to a particular nursing unit or hospital, the SAFE Loop Team integrates information from incident reports, follow-up investigations, and internal and external sources, including an AHRQ PSO.

(5) Feedback to Nurses (Mitigation Phase): To demonstrate that reports are used and can drive system changes, the SAFE Loop Team provides feedback about medication safety problems and mitigation plans.

Implementation of Intervention on an Individual Nursing Unit:

Engagement Phase (4 weeks):

Obtain Input: Nursing units convene daily huddles with their staff to discuss various issues. For three weeks, the SAFE Loop Team will attend one huddle per week to provide information on local safety events and obtain input on problems that frontline nurses believe to be common, severe, and preventable.

To include nurses who work at night and on weekends, the intervention will be disseminated through nursing huddles, which occur at shift change. We will also place fliers approved by the Marketing Dept on tack boards in common areas like break rooms and conference rooms away from public areas.

Select Target Medication Events: Each study nursing unit will select its own unique event. Through discussions with nurses and the SAFE Loop Team, the Unit Manager will choose a medication safety problem with a narrow enough scope to facilitate mitigation through targeted actions (e.g., problems

with opioids). The SAFE Loop Team will define inclusion/exclusion criteria for the unit's Target Medication Event.

Fact-Finding Phase (12 weeks):

Train Nurses: The SAFE Loop Team will train nurses to: (1) submit reports on Target Medication Events (in addition to usual reports); (2) focus on unsafe conditions and near misses, and (3) write detailed narrative descriptions of circumstances they observed leading up to each event. The SAFE Loop Team will train Nursing Unit Managers in a just-culture approach (i.e., addressing system issues rather than blaming individuals).

Stimulate Reporting: The SAFE Loop Team will attend huddles weekly to ask nurses about Target Medication Events, remind them to submit reports, and reinforce how to write high-quality reports. A data analyst will provide quantitative data reports for review at the weekly huddles. Based on the pilot study, 12 weeks is long enough to collect enough reports but short enough to retain nurses' attention and facilitate rapid action.

To train nurses in how to write high-quality incident reports, the SAFE Loop Team will work with a nursing educator at Cedars-Sinai and develop content for a HealthStream module approved by the Chief Patient Safety Officer. This module will include a short set of slides with voiceover narration explaining the importance of focusing on a Target Event and the value of providing a detailed narrative description of events including contributing factors when filing reports. Completing the module will take no more than 10 minutes. All nurses on the study units will be delivered the module in their HealthStream accounts and asked to complete it; they will receive this request via usual channels of communication (e.g., email reminders). The information in the HealthStream module will be reinforced via visits by SAFE Loop staff to daily nursing huddles, reminders from nursing unit managers, and via a small laminated reminder card that can be affixed to the nurses ID badge.

Analyze and Investigate: This iterative process will involve the SAFE Loop Team and Nursing Unit Manager. First, the Incident Report Clinical Reviewer will examine incident reports to identify Target Medication Events. The SAFE Loop Team and Nursing Unit Manager will provide input on key terms used to search for Target Medication Events, confirm which events meet the definitions, and discuss insights from the reports. Next, the SAFE Loop Team and Nursing Unit Manager will work together on follow-up investigations, including "mini-root-cause-analyses" whereby the Safety Officer and Nursing Unit Manager discuss events and contributing factors with frontline nurses for 10 to 15 minutes during morning huddles. Depending on the event, additional steps may include reviewing medical records, staffing records, pharmacy reporting systems, and patient complaints, and working with representatives of diverse physician specialties and hospital departments.

Integrate Information: Concurrently, the Safety Champion will seek external information on the Target Medication Event, with assistance from the Institute for Safe Medication Practices. The Safety Champion will access resources from ISMP, the National Alert Network by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), other AHRQ PSOs relevant to medication safety (Alliance for Patient Medication Safety, ECRI, CHPSO), the American Society of Health-System Pharmacy, the Institute for Healthcare Improvement, the Collaborative Alliance for Nursing Outcomes, AHRQ's PSNET, the Joint Commission, and the FDA. Next, the Safety Champion will integrate information from incident reports, internal investigations, and external resources to draft a synopsis of the Target Medication Events, contributing factors, and any mitigation strategies used elsewhere. The SAFE Loop Team and Nursing Unit Manager will edit the synopsis for relevance and clarity. The Nursing Unit Managers will share it with frontline nurses through email and the huddles.

Action and Feedback Phase (16 Weeks):

Develop Plan: The SAFE Loop Team and Nursing Unit Manager will employ the information summarized in the synopsis to develop a mitigation plan that involves system changes such as protocols, practices, equipment, staffing, and oversight (not *solely* educating providers). Ideally, stronger actions, such as process changes and hard stops, will be implemented. Where possible, they will draw from prior interventions on other nursing units or in other hospitals. To assure that the mitigation plan is feasible and aligned with clinical practice, the Safety Champion will elicit ideas from nurses on the unit. The SAFE Loop Team will discuss advantages and disadvantages of promising strategies, then the Nursing Unit Manager and Safety Officer will establish the final plan. Where necessary, the Safety Officer will coordinate with other departments and senior hospital leaders.

Distribute Feedback: The Safety Champion will draft a summary of the mitigation plan and obtain feedback. The Nursing Unit Managers will share the mitigation plan with frontline nurses through email and the huddles.

Implement and Sustain Plan: The Nursing Unit Manager will take local actions to improve systems of care, assure that the planned changes are implemented, and make any subsequent refinements through ongoing Plan-Do-Study-Act cycles. The Safety Officer will help to overcome any barriers, assure alignment with other departments, and involve senior hospital leaders when necessary. The SAFE Loop Team will visit the nursing unit weekly during a 6-month follow-on period to reinforce and facilitate refinements to the plan.

Table: Roles in the Existing Reporting System and the SAFE Loop Intervention

	Position	Roles in Existing Reporting System	ADDITIONAL Roles in SAFE Loop Intervention
	Nurses on Study Nursing Units	Spontaneously submit incident reports. Use the SBAR (situation, background, assessment, and recommendation) structure when writing reports.[9]	Provide input on the Target Events, undergo training in reporting, submit reports, receive feedback, and implement mitigation strategies.
	Nursing Unit Managers	Administratively responsible for overseeing efforts to improve the safety of care on each nursing unit. Participate in analyzing reports, conduct any investigations, design and implement any solutions.	Select the Target Medication Events and work with the SAFE Loop Team throughout implementation. (Nursing units will be the unit of randomization and are defined by having a unique Manager).
SAFE Loop Team	***Incident Report Clinical Reviewer***	Classifies events, assigns harm severity, identifies source nursing unit, and triages high-risk events to relevant departmental and unit leaders.	Identifies and extracts information from reports on Target Medication Events. (Different reviewers will assist intervention and control nursing units).
	Safety Officer	Assists nursing units with investigations, obtains resources, engages leaders of relevant departments, and overcomes barriers. Oversees root-cause analyses of harmful events.	Directs the SAFE Loop Team. Facilitates investigation of near misses. (Different Safety Officers will assist intervention and control nursing units).
	Safety Champion	Not applicable.	Obtains input from and trains nurses, assists with investigations, integrates information from reports and other sources, drafts feedback to nurses.
	AHRQ Patient Safety Organization	Not applicable.	Institute for Safe Medication Practices (ISMP) serves as a resource to the SAFE Loop Team, providing information on events at other hospitals.

6.1.2 DOSING AND ADMINISTRATION

Not applicable

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Random Sequence Generation, Allocation Concealment, and Blinding: A researcher (not on the SAFE Loop or Data Collection teams) will use computer-generated random numbers to randomly assign the 4 nursing units within each of the 5 randomization blocks to one of 4 study groups, reflecting 2 arms (intervention and control) and 2 periods of time (sequential implementation; see Table below). Next, the researchers will place lists of the nursing units assigned to each group in opaque, sealed envelopes labeled with group numbers. At the start of each implementation period, the SAFE Loop Team will open the corresponding envelopes to determine the 5 nursing units that are assigned to each group. Research staff involved in data collection will be blinded to which nurses and patients are assigned to which arm.

Table: Study Design, Including Study Arms and Measurement Periods

Group	½ Year 1	Year 2	Year 3
1	Baseline b	**SAFE Loop** f i Follow-on	
2	Baseline b	Control f Follow-on	
3		Baseline b	**SAFE Loop** f i Follow-on
4		Baseline b	Control f Follow-on

Light green = baseline measurement periods for Aims 1 & 3

Orange = baseline (b) and follow-up (f) survey deployments for Aim 2

Dark blue = SAFE Loop arm

Medium blue = control arm

Yellow = qualitative interviews (i) on implementation and follow-on period

Dark green = follow-on period for Aim 3

6.4 INTERVENTION COMPLIANCE

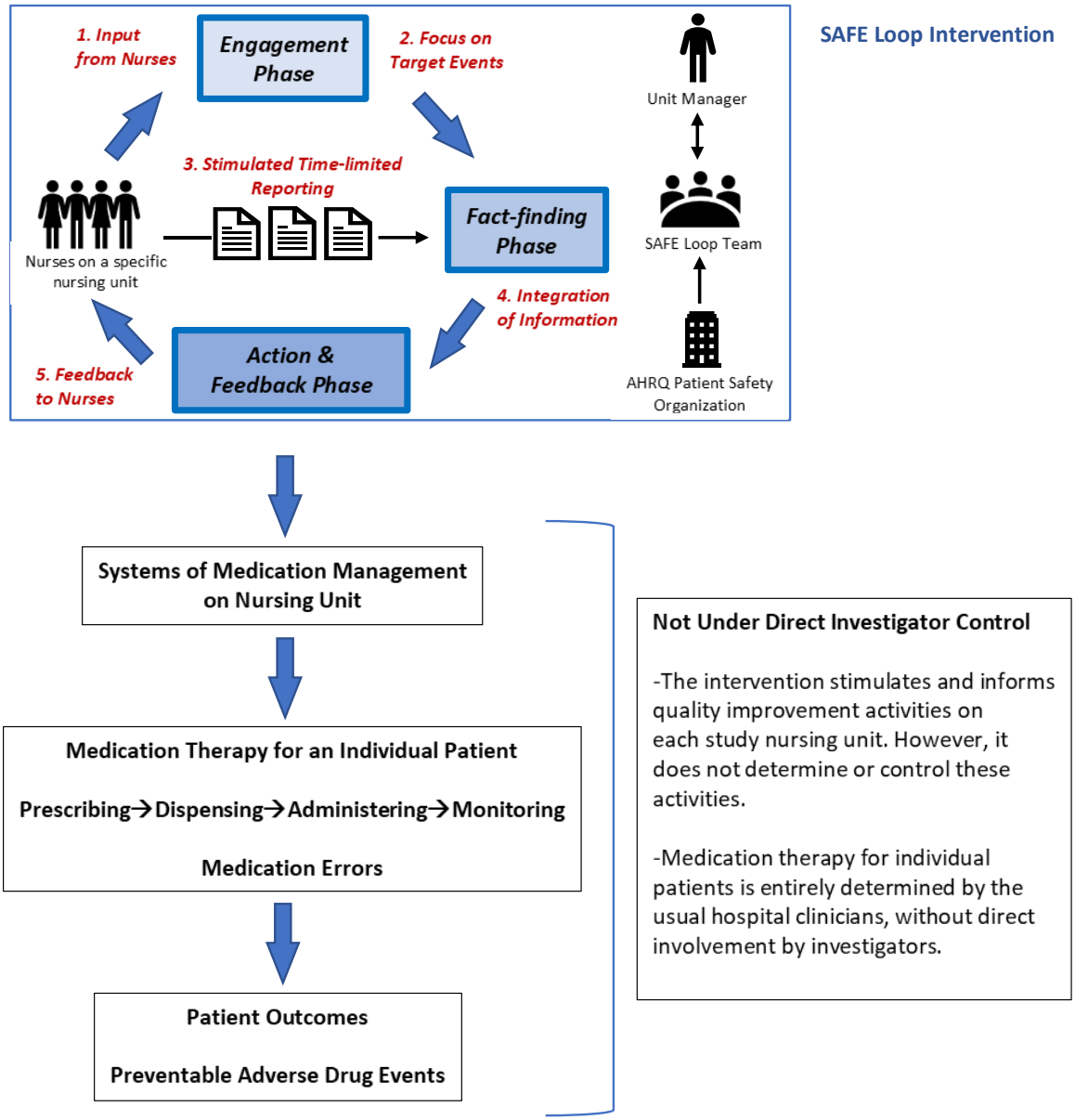
Implementation Processes*:* Importantly, this is a quality improvement intervention that will be implemented flexibly by hospital staff and not a rigid protocol to which they must comply. The Chief Patient Safety Officer (Dr. Seferian), will oversee implementation of the SAFE Loop, given his extensive prior experience implementing other performance improvement interventions. *Planning:* During year 1, the research team will refine the implementation plan, which considers stakeholders' needs, tailors the SAFE Loop for subgroups (e.g., nurses vs. unit managers), employs appropriate communication channels (e.g., daily nursing huddles), and tracks progress toward milestones. *Engaging:* Engagement is fundamental to the SAFE Loop, particularly nurses' input on medication safety problems, participation in "mini-root-cause analyses," and receipt of feedback. *Executing:* SAFE Loop Team members will reinforce the SAFE Loop via stimulated reporting and feedback. Nursing Unit Managers will serve as local implementation leaders, and each nursing unit has one or more additional nurses designated as Safety Representatives who will assist with this process. *Reflecting and Evaluating:* We will perform a detailed qualitative analysis of implementation.

The SAFE Loop intervention is designed to shape but not constrain or determine or control systems of medication management on each nursing unit. These systems of medication management, in turn, influence but do not constrain or determine how individual clinicians provide care to individual patients. The care provided to individual patients can, unfortunately, involve medication errors. Medication

errors are problems with the ordering, dispensing, administration, or monitoring phases of medication therapy. Patient outcomes resulting from medication errors are influenced by the errors themselves as well as patient characteristics including the reason for hospitalization, the set of medications, age, gender, comorbidities, and diverse other factors.

Under the SAFE Loop, the goal is to have nurses use incident reports to identify problems with systems of care on the nursing units and then develop and implement changes to those systems of care that reduce the likelihood of medication errors. As indicated by the diagram below, the SAFE Loop intervention has the potential to influence systems of medication therapy, care for individual patients, and patient outcomes, but these are not under direct investigator control.

Relationship between Intervention, Systems of Care, Care for Individual Patients, and Outcomes



6.5 CONCOMITANT THERAPY

Not Applicable

6.5.1 RESCUE MEDICINE

Not Applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The DSM will be able to interrupt the trial if there are serious concerns about data safeguarding or safety based on potential adverse events or other information, and if there have been any adverse events (particularly serious events). The study team will work with the DSM to develop rules for stopping the trial, based on the occurrence of severe adverse events.

Discontinuation of the SAFE Loop intervention does not necessarily mean discontinuation of the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified in a participant or one arm (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The SAFE Loop intervention is implemented at the level of the nursing unit. Additionally, the nursing units choose how to modify systems of medication therapy to improve safety, and those local changes can be considered hospital quality improvement interventions. As such, individual nurses and patients do not have the ability to withdraw from the study. However, nurses can choose not to engage in SAFE Loop activities such as filing incident reports on Target Medication Events. Nurses can also decline to respond to the survey under Aim 2. No data are collected directly from patients.

7.3 LOST TO FOLLOW-UP

Not applicable. We will have complete data on all patients who receive care on the study nursing units. If nurse choose not to complete the survey, this will not constitute “loss to follow-up.”

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Methods for Aim 1: Incident Reporting Practices

A. Measures: There are two key outcome measures and several descriptive measures. One key outcome measure is the *rate per 1000 patient-days of incident reports addressing one of the Target Medication Events*. Ten nursing units will implement the SAFE Loop, leading to 10 Target Medication Events total.

The primary outcome measure will be *the number of system plus human factors per incident report*. In industries where incident reporting has been effective, obtaining insights into contributing system and human factors has been the purpose of reporting. To *characterize system and human factors*, we will use the Human Factors Analysis and Classification System for Healthcare (HFACS-Healthcare).[44] Introduced in 2001, the HFACS has widely been widely used to analyze incidents in diverse industries internationally.[44-47] More recently, HFACS developers adapted it for use in healthcare settings.[48] HFACS-Healthcare lists 21 categories of contributing factors within 4 tiers (**Table 6**).[9] We will also examine the number and diversity of factors reported.

Table 6: Incident Report Characteristics
Contributing Factors (HFACS, 4 tiers)
Organizational influences (system factors)
Unsafe supervision (system factors)
Preconditions for unsafe acts (system)
Unsafe acts (human factors)
Severity (NCC MERP, 9 Categories)
A: Safety hazard (did not involve patient)
B: Event did not reach patient
C: Event reached patient, no harm
D: Monitoring/intervention to prevent harm
E: Temporary harm requiring intervention
F: Temporary harm, prolonged hospitalization
G: Permanent harm
H: Intervention to sustain life
I: Death
Preventability (Brook et al.)
Definitely or probably preventable
Definitely or probably not preventable
Uncertain/unable to determine (added)

Descriptive Measures*:* Patient factors also represent opportunities to improve care. To classify *patient factors*, we will use categories from prior work.[4] Experts consider severity and preventability when prioritizing incidents for follow-up and action.[49] To classify *severity*, we will use the NCC MERP Medication Error Index.[50-52] To classify *preventability*, we will adapt an existing scale.[53]

Data Collection: Analysts with clinical experience (e.g., nursing, pharmacy) and training in HFACS-Healthcare will manually review incident reports related to medication issues. Pairs of analysts will independently judge whether each incident matches one of the definitions of Target Medication Events, extract information related to the measures above, and then meet to discuss and reach consensus. A human factors expert (Dr. Cohen) will adjudicate any ties. Analysts will be blinded to nursing unit, time period, and study arm. Data collection instruments will be adapted from our prior work.[4,9,54] As part of training, analysts will practice on at least 30 sample reports, consulting with each other and the human factors expert until scores are consistent. To evaluate reliability, we will calculate Cohen's Kappa for 10% of records.

Methods for Aim 2: Nurses' Attitudes toward Incident Reporting

Measures: The planned outcome measures include two composite measures from the AHRQ Hospital Survey on Patient Safety (SOPS) Culture™, Version 1.0 (English). AHRQ developed the survey in 2004 to assess the perspectives of frontline providers and staff on patient safety, error, and event reporting. Since then, hundreds of hospitals across the U.S. and internationally have used it. The survey has moderate-to-strong validity and reliability,[55] and the items and dimensions are psychometrically sound at the individual, unit, and hospital levels.[56] A 2015 systematic review found associations between Hospital SOPS scores and patient outcomes at hospital and nursing-unit levels of analysis.[57] Scores represent percentages (range 0-100%, higher is better). Changes in overall Hospital SOPS scores of 8.6 percentage points (range, 6.5-10.6) have been associated with changes in practices by hospital leaders.[58]

Table 8: Hospital Survey on Patient Safety (SOPS) Culture, Including Data from Study Site (CSMC) and Nationally		
12 Composite Measures	**CSMC**	**National**
Feedback & Communication About Error	75%	68%
Frequency of Events Reported	72%	67%
Communication Openness	63%	64%
Handoffs & Transitions	52%	46%
Management Support for Patient Safety	72%	73%
Nonpunitive Response to Error	35%	44%
Organizational Learning	83%	73%
Overall Perceptions of Patient Safety	70%	66%
Staffing	49%	53%
Supervisor Expectations & Actions	74%	79%
Teamwork Across Units	66%	61%
Teamwork Within Units	84%	82%

The survey takes 10-15 minutes to complete and includes 42 items used to derive 12 composite measures (**Table 8**), 2 single-item measures, and respondents' backgrounds (unit, staff position, interaction with patients, years of experience in current profession, hospital, and current nursing unit). Most items are scored on a scale from 1 (strongly agree) to 5 (strongly disagree). Creating composite scores involves: (1) inverting the scales of any negatively worded items, (2) identifying positive responses (1 or 2); (3) calculating the percent of responses that were positive for each item (excluding missing values), and (4) averaging the percent positive across all items within a composite measure.

The two composite measures we plan to use are directly relevant to incident reporting and likely to be responsive to system-level changes. *Feedback and Communication About Error* includes three items: staff are informed about errors, discuss ways to prevent errors, and are given feedback about changes implemented. The *Frequency of Events Reported* also includes three items: staff report mistakes that are caught before affecting the patient, with no potential to harm, and that could harm but did not. In a prior analysis from three nursing units at three different hospitals, scores on these two composite measures were correlated (ρ=0.56) but factor analyses indicated that they captured distinct concepts (loaded separately). Respectively, Cronbach α values for these measures were 0.77 and 0.78 among nurses, demonstrating good internal consistency.[55]

B. Data Collection: Cedars-Sinai routinely surveys staff every two years using the Hospital SOPS. For the study, we will survey ~1980 eligible nurses on study nursing units twice via 4 total deployments of the full Hospital SOPS during two-week intermissions between study periods (Section 3A). To identify eligible nurses, we will obtain staffing databases including names, email addresses, title/position, percent effort, dates of work on the unit, and work schedule. At least 85% of nurses on study units will be eligible. Two weeks before deployment, we will send email notices to expect the survey and a researcher will visit nursing units to reinforce survey completion. The survey will be delivered via REDCap using a weblink embedded in an email. During each deployment, we will deliver the survey three times. We will incentivize completion at the individual (lotteries for iPads) and unit levels (gift baskets of snacks for response rates >65%). To minimize detection bias, the survey will not refer to the SAFE Loop intervention. To avoid having incomplete outcome data, we will monitor survey response rates and make adjustments to procedures as needed.

Methods for Aim 3: Rates of Target Medication Events

A. Measures: The primary outcome will be the *rate per 1,000 patient-days of Target Medication Events (preventable plus potential adverse drug events)* selected by the 10 nursing units in Groups 1 and 3. We will also examine the rate of events involving harm. We will define events as in prior research (**Table 10**).[38,61,62]

Table 10: Medication Event Definitions			**Examples**
ADE (NCC MERP severity E-I)		A patient injury* resulting from a medical intervention related to drug(s).	A rash due to an antibiotic.
	Preventable	An adverse drug event due to a medication error.†	A rash due to an antibiotic given despite known allergy.
	Non-preventable	An adverse drug event not due to an error.	A rash occurring after first exposure to an antibiotic.
Potential ADE		A medication error that had the potential to cause injury but did not.	
	Intercepted (NCC MERP B)	A medication error that was detected and stopped before the patient received the medication.	A pharmacist filling orders discovers a known allergy and prompts the prescriber to switch antibiotics.
	Non-intercepted (NCC MERP C-D)	A medication error in which the patient received the medication but did not to experience harm.	A patient with a known allergy to an antibiotic receives the drug anyway but does not develop a rash.

*An injury is an unintended consequence of care that negatively affects a patient's health and/or quality of life. † A medication error is an error anywhere in the process of drug ordering, dispensing, administration, and monitoring.

Descriptive Measures: We will characterize event *severity/harm* (NCC MERP categories), *medication class* (e.g., cardiovascular, diabetes, etc.), and *route of administration* (intravenous, oral, etc.). We will classify any errors by *stage in drug therapy* (ordering, dispensing, administering, monitoring), *profession(s)* involved (physician, pharmacist, nurse, other), and *error types* (allergy, drug-disease interaction, drug-drug interaction, drug-lab interaction, duplicate therapy, therapeutic omission, concentration, duration, route/dosage form, dose/frequency/rate, wrong medication, wrong patient, wrong timing, incomplete order).[5,6,38,61] We will asses which events are *Target Medication Events* used by Group 1 and 3 nursing units (yes, no; and which unit).

B. Data Collection: The nursing units will implement mitigation plans designed to prevent Target Medication Events toward the end of the SAFE Loop implementation (Section 2B), which means that medication events will not start to fall until after that. Accordingly, we will monitor medication events during a baseline period, the implementation period, and 6-month follow-on period after implementation (Section 3A). To identify medication events, we will randomly sample 1,520 hospitalizations divided equally between the four study groups and the baseline and follow-on periods. (We will exclude the emergency department from Aim 3).

To detect medication events, we will employ the widely accepted Trigger Tool Method by Institute for Healthcare Improvement. It involves two stage: (1) nurses systematically screen medical records for "triggers" (clues that an event occurred) and write synopses of possible events, and (2) physicians review synopses to confirm and classify them. Many studies have used these methods, including studies by Dr. **Nuckols**.[5,6,38,61-64]

Screening: Research nurses will search for several types of triggers including the use of medications that can counteract other medications (e.g., naloxone), abnormal lab results (e.g., serum glucose <50 mg/dL), clinical events (e.g., rash), abrupt cessations of medication, and transfers to a higher level of care.[52] To increase our ability to detect potential ADEs, we will add an additional "trigger": events in the Cedars-Sinai "Ivents" database, where pharmacists routinely record changes to medication therapy made to reduce the risk of harm (overseen by Dr. **Leang**). Ivents reports are distinct from voluntary incident reports (we will not include regular incident reports). Two research nurses will perform these screenings, blinded to study arm. To train the nurses, we will adapt training manuals and procedures from the Institute for Healthcare Improvement and our prior research.[5,6,52] Manuals will include descriptions of the Trigger Tool method, Ivents reports, and variables employed in classifying the medication events. Through a 3-day in-person training session, nurses will become familiar with the manuals, ask questions, review 3 sample charts with supervision (by Dr. Nuckols), review an additional 5 to 7 sample charts independently, and then meet with the trainer assess proficiency. During data collection, quality monitoring and training reinforcement will occur in two ways (1) the research nurses will submit questions and maintain a log of trainers' responses, and (2) physician reviewers will ask for clarifications when the event synopses lack essential information. To obtain potential covariates for use in regression models, nurses will also extract patient age, gender, race, ethnicity, discharge diagnosis codes needed to score the Elixhauser comorbidity index, and primary and secondary payer. To ascertain reliability (Cohen's kappa statistics), a randomly chosen 10% of medical records will undergo duplicate review.

Classification: Two physicians will independently review each synopsis, employing a standardized rating form that includes the variables above. Next, they will meet to discuss responses. When there are discrepancies, physicians may ask the research nurses for additional information or involve a third physician to break ties. To ensure blinding, synopses will not include identities of patients, clinicians, or

nursing units. For training, physicians will receive similar manuals as the nurses and score 20 sample events with an experienced reviewer (Dr. Nuckols). We will select 10% of synopses to calculate interrater reliability (Cohen's kappa).

Qualitative Analysis of Implementation: If the SAFE Loop improves outcomes, understanding how and why it worked will enable the intervention to be improved and adapted for use at other hospitals as well as at Cedars-Sinai. Similarly, if the SAFE Loop is ineffective, insights into its limitations will reveal how incident reporting systems could be improved through other types of changes.

A. Data Collection: After SAFE Loop implementation, we will conduct one-on-one in-person interviews with 10 Nursing Unit Managers and 22 frontline nurses. This sample size will enable us to perform purposive sampling to acquire broad representation by randomization block, study group, and nursing unit. Interviews will occur in locations convenient to interviewees, last approximately 30 minutes, and be audio recorded (with permission). We will recruit interviewees by visiting nursing huddles. Participants will be entered into a lottery for an iPad. We will use a semi-structured interview guide with open-ended questions and follow-up probes to examine several topics, including: fidelity to SAFE Loop as planned, adaptations to SAFE Loop, SAFE Loop "dose" (e.g., did nurses learn about it once or several times?) and "reach" (e.g., were all nurses on the study units aware?), facilitators/barriers to implementation, mechanisms of action (e.g., did nurses respond to providing input, receiving guidance on how to report, or emphasizing near misses?), exposure to the SAFE Loop in the control arm, and contextual factors that may have moderated its effectiveness. Finally, we will discuss how to adapt the SAFE Loop for ongoing use over the long term and how to enhance its effectiveness.

B. Analysis: Interviews will be transcribed from audio recordings, with personal identifiers removed. Pairs of researchers trained in qualitative analysis will analyze transcripts in Dedoose using a combination of content-analysis and qualitative inquiry, allowing them to discover and quantify the nurses' experiences and perceptions. We will use an iterative process to identify *a priori* themes based on the domains above, and to create *in vivo* themes as they emerge during coding (e.g., specific barriers to implementation).[65] The two coders will code each interview independently and then discuss variations until consensus is reached. After coding all interviews, we will use the constant comparative method to combine similar themes with limited data under more general themes.[66] In the final step of analysis, we will review Dedoose code reports (participant N and density) of salient themes and coding matrices related to significant interview findings.

8.1.1 UNANTICIPATED PROBLEM REPORTING

The principal investigator (PI) will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 days of the investigator becoming aware of the event, to allow the investigator to conduct an investigation.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 days of the IRB's receipt of the report of the problem from the investigator.

8.2 SAFETY AND OTHER ASSESSMENTS

The level and frequency of monitoring are designed to be commensurate with the risks, nature, and complexity of this clinical trial. Additionally, the data safeguarding procedures will adhere to all current standards established under the Common Rule, the Health Insurance Portability and Accountability Act (HIPAA), policies by AHRQ and NIH, and policies established by the Cedars-Sinai Institutional Review Board. All investigators have undergone required trainings in human subjects' protections and have extensive experience in handling sensitivity information. As PI, Dr. Nuckols has ultimate responsibility for monitoring data and safety.

Monitoring procedures will serve the following functions: (1) reviewing the research protocol and plans for data and safety monitoring issues; (2) monitoring data quality, timeliness, survey response rates, and factors that may affect the risks and benefits of the study such as emerging literature; (3) monitoring for potential and actual adverse events, and (4) making recommendations regarding continuation of the trial.

Internal Monitoring Procedures: The study team will learn of potential issues with data and safety for nurses and patients through the following procedures.

Nurses: Dr. Coleman will meet periodically with nursing unit managers to qualitatively monitor nurses' perceptions of the study, including whether they have any concerns or any potential or actual adverse events have occurred. As Chief Patient Safety Officer, Dr. Seferian will monitor for increases in the number of referrals of nurses to the Human Resources Department on the intervention nursing units during the study period. Additionally, the Analytical Team will monitor responses to a relevant domain on the AHRQ Hospital Survey on Patient Safety Culture, Nonpunitive Response to Error, which reflects whether nurses feel that they have been blamed for reported incidents. This survey will be deployed before and after the implementation of the SAFE Loop, enabling the research team to detect problems with the first implementation phase before the subsequent phase begins.

Patients: Dr. Coleman will work with the Cedars-Sinai Patient Safety Department, which handles incident reports, to qualitatively monitor whether there may be any reports addressing risks to patients associated with changes in practice on study nursing units that were implemented in response to the intervention.

Inadvertent Disclosures of Identifiable Information: The team will self-monitor whether data are collected, stored, transmitted, and analyzed in accordance with the Data and Safety Monitoring Plan and for any inadvertent disclosures of sensitive information.

The research team will include data and safety monitoring on the agenda of each routine team meeting, enabling any concerns to be identified and addressed quickly. The study will submit annual progress reports to the Cedars-Sinai Institutional Review Board and meet annually with the external DSM during Years 1 to 4.

External Monitoring Procedures: The DSM will monitor throughout the portions of the study that involve human subjects, including implementation of the SAFE Loop, surveys of nurses, and extraction of data from incident reports and medical records. The DSM will meet with the Executive Oversight Team four times via teleconference to review the Data and Safety Monitoring Plan, proposed study procedures, data safeguarding practices, and data on potential and actual adverse events.

- *Year 1:* The DSM will meet to review study protocols and the Data and Safety Monitoring Plan prior to the start of data collection.
- *Year 2:* The DSM will meet to monitor progress in the study and consider any new information related to risks to nurse and patients. This meeting will represent a project milestone (see timeline) because it will provide a more complete picture of the risks associated with the study.
- *Year 3:* The DSM will meet to monitor progress and any potential or actual adverse events. Additionally, the study Analytical Team will send the external monitoring body the survey responses on Nonpunitive Responses to Error after each deployment of the survey.
- *Year 4:* The DSM will meet after the intervention and data collection are complete to review information on potential or actual adverse events. This meeting will represent a project milestone (see timeline) because it will be the concluding meeting of the DSM.
- *Additional Reviews:* The DSM will reserve the right to request additional interim reviews, in the unlikely event that concerns are raised about data safeguarding or safety.

Investigation of Suspected Adverse Events: Any potential or actual adverse events will be immediately reported to Dr. Nuckols (PI) and Dr. Coleman (internal DSM). Dr. Coleman will contact the parties involved to investigate: (1) nature of the event, (2) the type and severity of harm, (3) potential attribution to the research study, (4) circumstances that led up to the event including whether any study procedures deviated from the study protocol, and (5) potential for recurrence. Dr. Coleman will report this information to the research team, which will discuss how to address the event and to reduce the risk of recurrence.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Nurses:

- *Loss of professional reputation:* Adverse job consequences for a nurse due to study participation, such as having documentation of providing suboptimal care placed in employment/human resources files, will be considered a serious adverse event.
- *Economic harm:* Adverse job consequences for a nurse due to study participation, such as 1) having work hours reduced, 2) being passed up for a professional opportunity, or 3) being dismissed from Cedars-Sinai, will be considered a serious adverse event.
- *Disclosure of individually identifiable information:* Evidence of significant psychological or other harm to nurses due to disclosure of individually identifiable information outside of the study team will be considered a serious adverse event.
- *Psychological distress:* If a nurse reports psychological distress due to study participation (e.g., via loss of professional reputation or economic harm) that interferes with functioning on a prolonged basis or warrants referral to a mental health professional, this will be an serious adverse event.

Patients:

- *Medication error:* A medication error resulting from the SAFE Loop that required caused a patient temporary or permanent physical harm (a preventable adverse drug event) will be considered a serious adverse event.
- *Disclosure of individually identifiable protected health information:* Evidence of significant psychological or other harm to patients due to disclosure of individually identifiable information outside of the study team will be considered a serious adverse event.

8.3.2 CLASSIFICATION OF AN ADVERSE EVENT

8.3.2.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** –
  - Events that do not interfere with the participant's daily activities, cause significant distress, or interfere with major life functions.
  - Medication errors that require minimal or no treatment (NCC MERP categories B and C).
- **Moderate** –
  - Events that cause inconvenience, interference with functioning, disruption of usual daily activity, or greater worry or concern.
  - Medication errors that require monitoring and/or intervention to prevent harm (NCC MERP categories D and E).
- **Severe** –
  - Events that significantly interrupt a participant's usual daily activity, cause distress, or interfere with major life functions.
  - Medication errors that prolong hospitalization, are potentially life-threatening, are incapacitating, or are fatal (NCC MERP categories F to I).

8.3.2.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the intervention and/or study procedures must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.2.3 EXPECTEDNESS

The Principal Investigator and Chief Safety Officer will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

- Events that are judged to be "related" to the SAFE Loop should be, at a minimum, temporally linked to the filing of an incident report for a Target Medication Event during the intervention period in an intervention nursing unit.
- Alternatively, medication errors that are judged to be "related" to the SAFE Loop should generally occur during the latter part of the "SAFE Loop" period (when the intervention designed to prevent medication errors is designed and implemented) or the "follow-on" intervention period. It should occur in an intervention nursing unit and match the definition of a Target Medication Event, as well as have features suggesting that they were caused by the changes on the nursing unit made in response to the SAFE Loop.

All AEs not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of occurrence, an assessment of severity, relationship to study (assessed only by those with the training and authority to make this assessment), and time of resolution/stabilization. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

8.3.4 ADVERSE EVENT REPORTING

The study team will report any potential or actual adverse events to the Cedars-Sinai Institutional Review Board and the external DSM within 7 days, to allow time to begin to investigate the event. A final report adjudicating the nature and severity of the event and relationship to the intervention will be provided to the IRB and external DSM within 30 days.

The team will respond to any adverse events with a written mitigation and prevention plan to avoid recurrence, and consider whether doing so may be beneficial following any potential adverse events. This plan will be developed within 60 days, to allow for a thorough understanding of circumstances leading up to the event.

8.3.5 SERIOUS ADVERSE EVENT REPORTING

If an event may meet criteria for being serious, the study team will report it to the Cedars-Sinai Institutional Review Board and the external DSM within 24 hours, while the investigation proceeds. Following the final adjudication of the event, the report will also be submitted to the AHRQ Project Officer.

8.3.6 REPORTING EVENTS TO PARTICIPANTS

In the event of disclosures of protected health information outside the research team, we will adhere with HIPAA and other regulations regarding notifying affected patients. Events will be reported to participants if deemed appropriate by Dr. Coleman (internal DSM), Dr. Nuckols (PI), the external DSM, or the Cedars-Sinai OHRP.

We will also report to nurses if individually identifying information of a sensitive nature is inadvertently disclosed outside the research team.

8.3.7 EVENTS OF SPECIAL INTEREST

Not Applicable

8.3.8 REPORTING OF PREGNANCY

Not Applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems will be reported to participants if deemed appropriate by Dr. Coleman (internal DSM), Dr. Nuckols (PI), the external DSM, or the OHRP.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Aim 1 Hypotheses:

1.1 The rate per 1000 patient-days at which nurses report incidents will increase more in nursing units engaged in the SAFE Loop than in units using the existing reporting system.

1.2 The number of system plus human factors per incident report will increase more in nursing units engaged in the SAFE Loop than in units using the existing reporting system. (Primary outcome for Aim 1)

Aim 2 Hypotheses:

2.1 Nurses' perceptions of feedback and communication about error on the nursing unit will improve more in nursing units engaged in the SAFE Loop than in units using the existing reporting system. (Primary outcome for Aim 2)

2.2 Nurses' perceptions of the frequency with which events are reported on the nursing unit will increase more in nursing units engaged in the SAFE Loop than in units using the existing reporting system.

Aim 3 Hypotheses:

3.1 The rate of medication events designated as high priorities will decline more in nursing units engaged in the SAFE Loop than in units using the existing reporting system. (Primary outcome for Aim 3)

3.2 The rate of medication events designated as high priorities and involving harm will decline more in nursing units engaged in the SAFE Loop than in units using the existing reporting system.

9.2 SAMPLE SIZE DETERMINATION

Aim 1:

On average per 6-month study period, each unit will provide 7,362 patient-days of care (294,470 pt-days/20/2) and submit 16.6 reports (665 reports/20/2). *H1.1.* The baseline rate is 2.26 incident reports per 1000 patient-days (665 reports/294,470). *H1.2.* Based on prior studies, the expected baseline number of system plus

Table 1: Minimum Detectable Difference in Outcome

Implementation trend	Betw-Cluster Coeff. of Variation			
	0.01	**0.05**	**0.10**	**0.20**
1.1. Incident Reports per 1000 Patient-days				
Yes	1.241	1.277	1.392	1.851
No	0.794	0.815	0.877	1.115
1.2. System plus Human Factors per Incident Report				
Yes	0.471	0.481	0.515	0.651
No	0.299	0.305	0.322	0.391

human factors is 0.70 per report.[1] **Table 1** presents the minimum detectable differences in outcomes as functions of the between-cluster coefficient of variation (CV) and the presence of implementation trend, using two-sided t-tests for Poisson rates with 80% power at 5% significance level. These differences would be meaningful to safety leaders, reflecting >35% increases in reporting rates and enhanced detection of the multiple contributing multiple factors that are typically involved in every error.

Aim 2:

Table 2: Minimum Detectable Difference in Outcome				
Implementation trend	**Intra-cluster Correlation**			
	0.01	**0.05**	**0.10**	**0.20**
Yes	10pp*	11pp	12pp	13pp
No	7pp	8pp	10pp	11pp

Power calculations are the same for both composite outcome measures. The baseline percentages of positive responses are 75% (*H2.1*) and 72% (*H2.2*). We assume 85% of 1980 nurses will be eligible and a 60% response rate (50.5 responses per nursing unit per deployment). We also assume a discrete uniform distribution for each composite measure with only four possible values (0%, 33%, 66%, 100%) per nurse because each measure contains 3 items. Therefore, we assume standard deviation (SD) equal to 37%, and a between-cluster coefficient of variation of 0.65 as recommended by Campbell and Walters.[2] The **Table** presents the minimum detectable difference in the percentage of positive responses as a function of the intra-cluster correlation (ICC) and presence of implementation trend, using a two-sided t-test for Normal means with 80% power at 5% significance level. Based on prior studies, a meaningful difference in the percentage of positive responses is 8.6 percentage points (pp).[3] Missing data patterns will be examined using the method proposed by Little[4] if the data is found to be not missing at completely random, missing values will be imputed with values drawn from fully conditional specifications using the multivariate imputation by chained equations (MICE) algorithm,[5,6] with the number of imputed datasets chosen such that the maximum loss of efficiency of 5%.[7] The plausibility of imputed values will be checked by corresponding diagnostics. The outlined statistical analysis will be performed for each imputed dataset and results will be pooled. All hypotheses will be two-sided at 5% significance level. Calculations will be performed using R-package, version 3.5.3.

[1] Nuckols TK, Bell DS, Paddock SM, Hilborne LH. Contributing factors identified by hospital incident report narratives. Qual Saf Health Care. Oct 2008;17(5):368-372.
[2] Campbell MJ, Walters SJ. How to design, analyse and report cluster randomised trials in medicine and health related research. John Wiley & Sons; 2014.
[3] Campione J, Famolaro T. Promising Practices for Improving Hospital Patient Safety Culture. Jt Comm J Qual Patient Saf. Jan 2018;44(1):23-32.
[4] Little RJ. A test of missing completely at random for multivariate data with missing values. Journal of the American Statistical Association. 1988;83(404):1198-1202.
[5] Audigier, V., White, I., Jolani, S. Debray, T., Quartagno, M., Carpenter, J., van Buuren, S. and Resche-Rigon, M. Multiple imputation for multilevel data with continuous and binary variables. Statistical Science 2018;33(2):160-183
[6] Resche-Rigon, M. and White, I. R. Multiple imputation by chained equations for systematically and sporadically missing multilevel data. Statistical Methods in Medical Research 2018; 27(6): 1634-1649
[7] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377-99.

Aim 3:

Table 3 presents the minimum detectable difference in event rates as functions of between-cluster coefficient of variation and implementation trend using a two-sided t-test for Poisson rates with 80% power at 5% significance level. A difference of 0.50 events per 1000 patient days is clinically meaningful, representing the avoidance of 147 events and 116 harmful events per year hospital-wide.

Table 3: Minimum Detectable Difference in Outcome

Implementation trend	Betw-Cluster Coeff of Variance			
	0.01	**0.05**	**0.10**	**0.20**
3.1 Target Event Rate				
Yes	0.766	0.929	1.292	2.108
No	0.516	0.631	0.886	1.474
3.2 Harmful Event Rate				
Yes	0.322	0.335	0.373	0.486
No	0.220	0.230	0.257	0.340

Qualitative Interviews:

Qualitative methods do not involve statistical tests or rely on calculations of statistical power. Instead, we provide a rationale for the proposed sample size and describe analytical methods.

After SAFE Loop implementation, we will conduct one-on-one in-person interviews with 10 Nursing Unit Managers and 22 frontline nurses. This sample size will enable us to perform purposive sampling to acquire broad representation by randomization block (there are 5 blocks), study group (there are four groups, with five nursing units per group – one from each block; half of the groups receive the intervention), and nursing unit (there are 10 nursing units that will be randomized to the SAFE Loop arm). Thus, we will interview one nurse manger and two nurses from each study nursing unit, about 6 per block, and 16 per group.

9.3 POPULATIONS FOR ANALYSES

The trial will randomize 20 nursing units to two arms: (1) the SAFE Loop, and (2) the existing reporting system (control). All analyses will compare data between these two arms.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will employ a cluster RCT to compare nursing units that implement the SAFE Loop, a system-level change in incident reporting, with nursing units that continue to use the existing reporting system. Outcomes will include changes in incident reporting practices, nurses' attitudes toward reporting, and rates of high-priority medication events. Qualitative interviews with nurses will provide insight into implementation. See Section 9.4.2 for detailed information describing the analytic plan.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Aim 1 Analyses*:*

Descriptive Analysis: We will perform descriptive analyses of reporting practices during the baseline periods and intervention periods, stratified by study arm. We will calculate rates of reported Target Medication Events and total reported medication events per 1000 patient-days (# of reports*1000/# of patient-days). Next, we will calculate the percentages of reported incidents in each NCC MERP category and the percentages of reports for which preventability could be determined. Finally, we will calculate

the number of contributing system, human, and patient factors per report and describe the types of factors reported.

Statistical Analyses: We will compare changes over time between study arms for: (a) rate of incident reports per 1000 patient-days, and (b) number of system plus human factors per report. Multivariable Poisson regression models will be fitted with response variables as (a) number of reports per patient, with offset given by the length of stay divided by 1000; and (b) number of system plus human factors per report. For both models, the main hypothesis is whether there is an interaction between study arm and time period (baseline, post-intervention). Nursing units will be divided between two implementation steps, creating the possibility of an implementation trend. Therefore, a three-way interaction among study arm, time period, and implementation step (Step 1: Group 1 and 2, Step 2: Group 3 and 4) will be tested. If this is statistically significant, results will be presented separately for each implementation step. Otherwise, implementation step will be an additive effect. Random effects will describe nursing units and models will adjust for demographics, Elixhauser comorbidity index, and primary payer (collected under Aim 3). All hypotheses will be two-sided at 5% significance level. Calculations will be performed in R-package, version 3.5.3.

Aim 2 Analyses:

Descriptive Analysis: We will calculate survey response rates, examine respondent characteristics (years worked in current profession, hospital, and current nursing unit and hours worked per week), and describe outcome measures (overall scores and composite measures) during each study period, stratified by study arm.

Assessment of Survey Measurement Properties: To evaluate the two selected composite measures' internal consistency, we will calculate Cronbach's α using data from baseline survey. To assess construct validity and convergent validity, respectively, we will evaluate associations (Pearson correlation coefficients) between scores on the composite measures and: (1) the full Hospital SOPS, and (2) incident reporting rates at the nursing unit level. To assess responsiveness, we will compare scores from baseline and follow-up surveys among nurses in the SAFE Loop arm (paired t-tests). If the composite measures do not demonstrate good internal consistency, construct, and convergent validity, we will use the full Hospital SOPS.

Statistical Analyses: We will compare changes over time between study arms for Feedback and Communication About Error and Frequency of Events Reported. Multivariable Normal regression models will be fitted for both endpoints and we will test hypotheses similarly to Aim 1. We will adjust for nurse characteristics from the AHRQ survey: years working in this hospital, years worked in current nursing unit, and hours worked per week. We will perform subgroup analyses by years of experience in current profession, because experience has been associated with medication error rates.[59]

Aim 3 Analyses:

Descriptive Analysis: We will calculate rates of preventable ADEs and potential ADEs per 1,000 patient-days, both overall and for the Target Medication Events for the Group 1 and 3 nursing units. We will describe the severity of the events, medication classes, errors, clinicians involved, and stages in drug therapy.

Statistical Analysis: We will compare changes over time between study arms for rates of (a) Target Medication Events per 1000 patient-days and (b) harmful Target Medication Events per 1000 patient-days. Multivariable Poisson models will be fitted with response variable as the number of (a) target medication events and (b) harmful medication events, with offset the length of stay divided by 1000

days. We will test hypotheses similarly to under Aim 1. Model covariates will include patient demographics, biological sex, Elixhauser comorbidity index, and insurance payer.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Qualitative Analysis of Implementation:

Qualitative interviews will be transcribed from audio recordings, with personal identifiers removed. removed. Pairs of researchers trained in qualitative analysis will analyze transcripts in Dedoose using a combination of content-analysis and qualitative inquiry, allowing them to discover and quantify the nurses' experiences and perceptions. We will use an iterative process to identify *a priori* themes based on the domains above, and to create *in vivo* themes as they emerge during coding (e.g., specific barriers to implementation).[65] The two coders will code each interview independently and then discuss variations until consensus is reached. After coding all interviews, we will use the constant comparative method to combine similar themes with limited data under more general themes.[66] In the final step of analysis, we will review Dedoose code reports (participant N and density) of salient themes and coding matrices related to significant interview findings.

9.4.4 SAFETY ANALYSES

Nurses:

- The Analytical Team will monitor responses to a relevant domain on the AHRQ Hospital Survey on Patient Safety Culture, Nonpunitive Response to Error, which reflects whether nurses feel that they have been blamed for reported incidents. This survey will be deployed before and after the implementation of the SAFE Loop, enabling the research team to detect problems with the first implementation phase before the subsequent phase begins.
- Dr. Coleman will meet periodically with nursing unit managers to qualitatively monitor nurses' perceptions of the study, including whether they have any concerns or any potential or actual adverse events have occurred.
- Dr. Seferian will monitor for qualitative increases in the number of referrals of nurses to the Human Resources Department on the intervention nursing units during the study period.

Patients:

- Dr. Coleman will work with the Cedars-Sinai Patient Safety Department, which handles incident reports, to qualitatively monitor whether there may be any reports addressing risks to patients associated with changes in practice on study nursing units that were implemented in response to the intervention.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Not Applicable

9.4.6 PLANNED INTERIM ANALYSES

Not Applicable

9.4.7 SUB-GROUP ANALYSES

We will perform two prespecified secondary analyses, stratifying by **biological sex** and age group (18-44, 45-65, over 65). Effectiveness may differ in these populations because Hug et al. found that 60.3% of preventable plus potential ADEs occur among women while 77.6% occur among adults age 65+.[61]

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not Applicable

9.4.9 EXPLORATORY ANALYSES

Not Applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

We are requesting a waiver of informed consent for implementation of the SAFE Loop intervention (both nurse and patients) and data collection procedures for Aim 1 (incident reports, both nurses and patients), and Aim 3 (adverse medication events, patients).

For nurses participating in Aim 2 (surveys) we are requesting a waiver of consent documentation. As the survey is via REDCap and is not collecting any identifiable information, requiring a signature would be the only link to a subject's identify. An information sheet will be provided with full consent information. Agreeing to complete and submit the survey will indicate their consent to participate.

For nurses participating in the qualitative interviews of implementation, we will provide consent forms describing in detail the study procedures and risks to the participant. Written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. For the survey, electronic consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The form will explain the research study to the participant and an FAQ will answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant

undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities (e.g., nursing interviews) will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at **in Redcap.** This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Cedars-Sinai research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Cedars-Sinai Medical Center.

Confidentiality Statute: Studies funded by the Agency for Healthcare Research and Quality are protected under the AHRQ Confidentiality Statute. This statute protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, this statute helps achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at **Cedars-Sinai.** After the study is completed, the de-identified, archived data will be destroyed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Internal DSM**
Teryl Nuckols, MD, MSHS, Vice Chair for Clinical Research, Director of General Internal Medicine	Bernice Coleman, PhD, ACNP-BC, Associate Director of Nursing Research and the Associate Director of the Nursing Performance Improvement Department
Cedars-Sinai Medical Center	Cedars-Sinai Medical Center
8700 Beverly Boulevard, Becker 113 Los Angeles CA 90048	8700 Beverly Boulevard, Room 1132 TSB Building Los Angeles CA 90048
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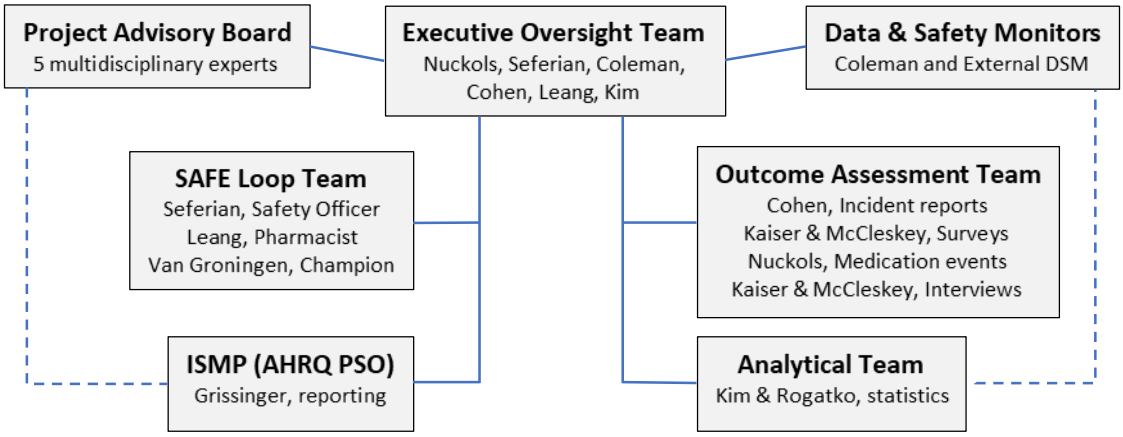
Executive Oversight Team: The organizational chart below shows the various roles of members of the study team. This team will be comprised of Dr. Nuckols (PI), Dr. Seferian (Chief Patient Safety Officer at Cedars-Sinai), Dr. Coleman (Associate Director of Nursing Research and of Nursing Performance Improvement), Dr. Cohen (Human factors expert), Dr. Leang (Pharmacist involved in medication safety at Cedars-Sinai) and Ms. Kim (Biostatistics and Bioinformatics at Cedars-Sinai). Dr. Nuckols will assume oversight and responsibility of all aspects of the project. Dr. Seferian will provide senior leadership from the perspective of implementing system changes designed to improve patient safety. Ms. Kim will provide senior expertise in the design of RCTs and statistical analysis. The other members of the advisory board will provide specific content expertise. All team members, especially the Executive Oversight Team and the DSMs, will safeguard data and monitor the safety of participants. The Data and Safety Monitors include an internal team member (Dr. Coleman) and an external Data and Safety Monitor (DSM, to be named).

Organizational Chart



SAFE Loop Team: The SAFE Loop team plays a key role in all aspects of the intervention, as described in the Approach section. This team will solicit input from nurses on study nursing units, train nurses to report Target Events, emphasize near misses, and describe circumstances leading up to events in detail. The team will partner with study units on the analysis and interpretation of events, as well as the development of a plan to mitigate events. The team will include Dr. Seferian as the Safety Officer, Dr. Van Groningen as the Champion, and an experienced analyst who routinely evaluates incident reports in the hospital.

Institute for Safe Medication Practices (ISMP): ISMP works with healthcare systems and practitioners to advocate for patient safety and promote safe medication practices. ISMP will serve as a resource to the SAFE Loop team during the analysis of reports and integration of events, and an ISMP staff member will also serve as a member of the Advisory Board. Finally, ISMP will assist with the dissemination of study findings via its usual channels for sharing the results of investigations of incident reports and for advancing medication safety nationally.

Advisory Board: We will recruit 5-7 national experts in incident reporting, human factors, medication safety, nursing care, and implementation science as well as a professional patient advocate to advise the project leaders at key junctures. The board will participate in one meeting before implementation to advise on compatibility with nursing practice, acceptability to nurses, and likelihood of improved safety, and overcoming barriers. After data collection is complete, the Advisory Board will discuss interpretation and dissemination of results, particularly adaptation of the intervention for use in other hospitals. Each meeting will last about 60 minutes, and there will be materials sent ahead to participants. Advisory Board members will only review aggregate information or completely de-identified qualitative information (e.g., a description of a medication safety event or a quote from an interviewee). They will not receive any sensitive or confidential data of any kind. Pursuant to discussions with the IRB, Advisory Board members will be considered external advisors, similar to a DSMB (so neither consent of the board members nor CITI training is required).

Outcome Assessment Team: This team will include both leaders who will direct each of the data collection efforts and support staff who will conduct the data collection. All data will be collected in a manner that blinds the assessors to the study arm.
Dr. Cohen will direct the extraction of data from hospital incident reports; she has a PhD in human factors and has applied the HFACS-Healthcare to incident reports at Cedars-Sinai previously. She will oversee two analysts with experience in patient safety and assure reliability in scoring.

Dr. Kaiser and Ms. McCleskey will oversee the deployment of the survey of nurses including assuring adequate response rates are obtained, and they will perform the qualitative interviews of nurses to examine intervention implementation. In addition, these two individuals will conduct qualitative analyses of implementation. Dr. Kaiser will provide senior expertise in qualitative methods, while Ms. McCleskey will oversee and perform day to day data collection activities.
Dr. Nuckols will direct the extraction of data on medication events from electronic medical records. She will train nurses and physicians in methods for screening for possible medication events and adjudication of such events, respectively. She will oversee three nurses and three physicians who will be blinded to the study arms.

Analytical Team: Sungjin Kim, MS and André Rogatko are statisticians with experience in experimental design including RCTs, psychometric analyses of surveys, biostatistics, and bioinformatics. They will: (1) coordinate statistical activities to ensure that investigators have ready access to statistical consultation and support, (2) provide statistical expertise in the design of experiments and studies, including research proposal development, sample size determination, and plans for interim reviews and final analysis, (3) assist with the writing of statistical components of manuscripts, (4) review the integrity and statistical soundness of all studies, (5) provide statistical analysis for all projects using appropriate statistical and computing methodologies, and (6) assist in the interpretation and presentation of results. Dr. Rogatko will advise Ms. Kim and the project team on advanced issues related to trial design and biostatistics.

10.1.6 SAFETY OVERSIGHT

Internal Data and Safety Monitor: Dr. Coleman has been designated as an internal Data and Safety Monitor because Dr. Coleman is a nurse with extensive experience in human subjects research. Dr. Coleman will be responsible for recruiting and interfacing with the DSM and for refining and maintaining the Data and Safety Monitoring Plan. In addition, she will oversee internal monitoring procedures, described below.

External Data and Safety Monitor (DSM): The DSM will be an expert in nursing and research ethics who is a single individual unaffiliated with Cedars-Sinai. The DSM will be tasked with independent oversight to monitor for adverse events, defined in Section 8.3.1. The DSM will review evidence of adverse events to recommend whether trials should be continued, altered, or terminated. We will recruit the DSM prior to randomization or data collection and convene meetings between the Executive Oversight Committee and DSM at designated points in the trial, in accordance with standard AHRQ and NIH procedures. The DSM will have no associations with the study team members or affiliations with Cedars-Sinai, and no conflicts of interest with study outcomes.

The Executive Oversight Team concluded that this pragmatic trial does not require a full Data and Safety Monitoring Board (DSMB) after conferring with the Cedars-Sinai Institutional Review Board and the UCLA Clinical and Translational Science Institute (CTSI) as well as reviewing a relevant publication.[8] Factors that argue against convening a full DSMB are: (1) recruitment and randomization are at the level of the nursing unit, obviating the need to monitor recruitment rates; (2) the intervention is a quality improvement intervention implemented at the nursing unit level with the support of the Cedars-Sinai

[8] Gregory E Simon, Susan M Shortreed, Rebecca C Rossom, Robert B Penfold, Jo Ann M Sperl-Hillen, Patrick O'Connor. Principles and procedures for data and safety monitoring in pragmatic clinical trials. *Trials.* 2019 Dec 9;20(1):690. doi: 10.1186/s13063-019-3869-3.

nursing and patient safety leadership; (3) the intervention has an indirect effect on patient care; treating clinicians retain full freedom and responsibility for making decisions in the care of individual patients (see Section 8.3.2.2); (4) the intervention poses a low risk of causing physical harm to study subjects; (5) study measures reflecting physical harm—rates of Target Medication Events—are collected retrospectively from existing data sources long after the care is provided, and it would be infeasible to detect a statistically significant increase in these events and shut down the trial in a timely manner; (6) other study outcome measures are not measures of physical harm but rather the behaviors and attitudes of clinicians. See Section 8.3 for additional information on Adverse Events.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Our research team at Cedars-Sinai will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

Our site will provide direct access to source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the research team under the supervision of Dr. Nuckols (PI). The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report

form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Redcap, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Procedures for Assuring Data Integrity and Confidentiality

Data safeguarding is the responsibility of the study PI as well as all individuals working with human subjects data on the research team. The PI will ensure the accuracy, completeness, and timeliness of the data reported as well as protect the data from inadvertent disclosure.

Data Management: Research data will be extracted into the Research Electronic Data Capture (REDCap) system, a secure, web-based application that supports data capture and management. REDCap (Research Electronic Data Capture) is a web application platform for creating and managing online surveys and databases. REDCap provides interfaces for data entry, audit trails for tracking data management and data cleaning and recoding activities, automated export procedures to common statistical software packages, procedures for important data from external sources, and standard methodsUsers can either create and design projects using 1) the online method from a generic web browser using the Online Designer; and/or 2) the offline method by constructing a 'data dictionary' template file in Microsoft Excel, which can be later uploaded into REDCap. Both surveys and databases (or a mixture of the two) can be built using these methods. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R). Also included are a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.[9]

REDCap is widely used for clinical research projects and has been adopted by the CTSI (Clinical and Translational Sciences Institute) consisting of Cedars-Sinai Medical Center (CSMC), University of California Los Angeles (UCLA), King Drew, and Harbor General as the tool for CTSI databases.

REDCap servers are housed at the CSMC Enterprise Information Systems (EIS) secure Data Center. The EIS Data Center is a modern facility with 24/7/365 power, cooling, connectivity, security and monitoring. Only authorized EIS Data Center staff have access to manage the physical servers. Security measures for the database include password management, inactivity logouts and maximum login attempts. Database/server TSM tape backups occur on a regular basis (daily and weekly) as per EIS NAS Backup Retention Schedule Policy and Tape Recall Procedure Policy (offsite secured storage).

Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected via Secure Sockets Layer (SSL) encryption to guard against unauthorized access to electronic protected health information (EPHI). Network security includes IP/ firewall restrictions, and SSL enabled web

[9] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42,377-81.

servers for https browser access. REDCap database meets the Health Insurance Portability and Accountability Act (HIPAA) Security Rule requirements. Appropriate administrative, physical, and technical safeguards are in place to ensure the confidentiality, integrity, and security of electronic protected health information (EPHI).

Assuring Data Integrity: All research staff who use REDCap will undergo training, and all data collection procedures will be monitored throughout the study period to ensure data quality and integrity. The Analytical Team will be responsible for receiving, reviewing, and cleaning all study data as well as generating regularly scheduled data quality reports and study status reports. Standardized reports will be developed during Year 1, during creation of the REDCap databases, and will be provided to the full study team and the Data and Safety Monitor at pre-specified times. These reports will include survey response rates for each study wave, progress on the analyses of incident reports and medical records, inter-rater reliability for those data extraction efforts, data quality concerns, and adverse events, and other elements requested by the study team. The Analytical Team will ensure secure data storage of verified and documented data, audit trails for data, and ensure back-up systems are working. Any missing or anomalous data will be referred to the respective Outcomes Assessment Teams for investigation.

Protecting Data from Disclosure: The study team will develop a detailed data safeguarding plan and submit it to the Cedars-Sinai Institutional Review Board and the Data and Safety Monitor and DSMB, if applicable. In brief, all data will be stored on secure, encrypted, password protected servers in locked facilities at Cedars-Sinai. Data transmission will be via secure, encrypted, password protected electronic interfaces. REDCap is a 21 CFR Part 11-compliant web-based database system. Only HIPAA-compliant Limited Datasets will be shared with the Analytical Team (containing dates and study identification numbers).

Details on Data Management by Study Procedure:

Data sources will include nurses' work schedules, surveys of nurses, incident reports, medical records, and qualitative interviews (audiorecordings and transcripts).

Work Schedules, Surveys, and Interviews with Nurses: The work schedules, surveys, and interviews with nurses will be individually identifiable (names, email addresses, possibly dates of birth) but will not contain sensitive information. To determine which nurses are eligible for the survey and interview procedures, we will obtain nurses' work schedules to ascertain how often the nurses work on a particular study nursing unit during the study waves of implementation and whether the nurses worked on the units for an entire study wave. If multiple nurses have the same name, we will use dates of birth and email addresses to distinguish them. We will distribute the survey via Research Electronic Data Capture system (REDCap).

Analysis of Incident Reports: The incident reports themselves constitute sensitive information for nurses and protected health information for patients. The data elements extracted from incident reports will not include individually identifiable information about nurses, but will include protected health information on patients and meet the definition of Limited Datasets under HIPAA. Data elements will pertain to the quality of incident reports and include incident dates and patient study identification numbers.

The analysts will obtain standard certifications in human subjects' protections and be trained to apply study instruments, use the electronic data collection interface, and adhere to study data protection procedures. Analysts will record the extracted data elements in a specially developed data collection interface in REDCap. Data extraction will be conducted by duplicate reviewers and then reconciled to

ensure data completeness and reliability. Analysts will conduct extensive pilot tests of study instruments using sample data sets until interrater reliability (agreement) as to scoring is very high.

To create patients study identification numbers to use the incident reporting dataset, the research team will create a master list of patient names, dates of birth, and unique identification numbers created using a random number generator. This linkage dataset will be maintained apart from other datasets and will be destroyed following the completion of the final paper from the study.

Analysis of Medical Records: Medical records include protected health information for patients. The data elements extracted will not include individually identifiable information about nurses, but will include protected health information on patients and meet the definition of Limited Datasets under HIPAA. Data elements will pertain to medication events (including medications, outcomes, errors, and dates of events, etc.), patient age, gender, race, ethnicity, medical comorbidities, and nursing units where the patient received care on each date in the study. In addition to patients electronic medical records, this data collection procedure also includes a pharmacy dataset called iVents, which captures issues related to medication orders.

Data extraction will occur in two stages. First, trained research nurses who work at Cedars-Sinai will manually extract data elements and draft summaries of any medication events; these summaries will include event dates and patient study identification numbers but no other identifiers, meeting the definition of a limited dataset under HIPAA. Second, trained physicians will review these summaries and classify the medication events. Both nurses and physicians will have standard certifications in human subjects' protections and be trained in data collection procedures. Both nurses and physicians will record the extracted data elements in a specially developed data collection interface in REDCap. The study team will conduct extensive supervised trainings (separately) for nurses and physicians, and require duplicate reviews of selected events to assess reliability. We will conduct extensive pilot tests of study instruments using sample data sets until nurse and physician interrater reliability (agreement) as to scoring is very high.

Qualitative Interviews: Researchers trained in qualitative methods will meet one-on-one with nurses who consent to interviews. With respondent permission, the interviews will be audiorecorded. Interviews will be transcribed from audio recordings, with personal identifiers removed from the transcriptions. Audiorecordings will be destroyed at the conclusion of the research.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the end of the study. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

Note that implementation of the intervention is designed to be flexible and is performed by hospital leaders, clinicians, and staff who bear the ultimate responsibility for patient care and patient safety, as noted in Section 6.4. Protocol deviations will NOT be considered noncompliance or reported, since they have only indirect effects on the care of individual patients.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers for 5 years after the completion of the primary endpoint by contacting Dr. Teryl Nuckols (PI).

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Agency for Healthcare Research and Quality have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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