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A study protocol for decreasing ICU-associated *Clostridioides difficile* infection through fluoroquinolone restriction: The FIRST trial

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Abstract

Introduction: Clostridioides difficile infection (CDI) is the most common healthcare-associated infection (HAI) in the USA, having high incidence in intensive care units (ICU). Antibiotic use increases CDI risk, with fluoroquinolones (FQ) particularly implicated. In healthcare settings, antibiotic stewardship (AS) and infection control interventions are effective for CDI control, but there is little evidence regarding the most effective AS interventions. Pre-prescription authorization (PPA) restricting FQs is a potentially promising AS intervention to reduce CDI. This study will evaluate the effectiveness of a FQ PPA intervention in reducing CDI rates in adult ICUs compared with pre-intervention care, and evaluate implementation effectiveness using a human-factors and systems engineering model.

Methods and analysis: This is a multisite stepped-wedge cluster effectiveness-implementation clinical trial. The trial will take place in 12 adult medical-surgical ICUs with ≥10 beds, Epic as electronic health record(EHR), and preexisting AS programs. Sites will receive facilitated implementation support over the 15-month trial period, succeeded by 9 months follow-up. The intervention comprises a clinical decision support system for FQ PPA, integrated into site EHRs. Each ICU will be considered a single site, and all ICU admissions included in analysis. Clinical data will be extracted from EHRs throughout the trial and compared to the corresponding pre-trial period, which will constitute the baseline for statistical analysis. Outcomes will include ICU-onset CDI rates, FQ days of therapy (DOT), alternative antibiotic DOT, average length of stay,

and hospital mortality. The study team will also collect implementation data to assess implementation effectiveness using the Systems Engineering Initiative for Patient Safety model.

Ethics and dissemination: The trial was approved by the Institutional Review Board at the University of Wisconsin-Madison (2018-0852-CP015). Results will be made available to participating sites, funders, infectious disease societies, critical care societies, and other researchers.

Trial registration: NCT03848689; Pre-results.

Article Summary

Strengths and limitations of this study

- FIRST will provide one of the few national, multi-site, comprehensive studies that investigate the effect on intensive care unit-associated-CDI of fluoroquinolone pre-prescription authorization integrated as a computerized decision support tool.
- Our trial design will allow us to look at changes in outcome measures over time at the same site, delineating a temporal sequence to ICU-associated and hospital associated CDI, providing more evidence for causality.

- Our approach simultaneously introduces antibiotic stewardship FQ prescribing best-practices, and assesses the introduction of these practices, facilitating continuous implementation improvement.
- The primary limitation to this trial is a slow-down in recruitment rates with the SARS-coV-2 Covid-19 pandemic, and the uncertain effects of this pandemic upon current ICU sites.

Keywords: Hospital associated *Clostridiodes difficile* infection, antibiotic stewardship, fluoroquinolone restriction, pre-prescription authorization, implementation effectiveness

Introduction

Background and rationale

Clostridioides difficile infection (CDI) is the most prevalent healthcare-associated infection in the United States[1] and CDI rates are consistently higher in intensive care unit (ICU) settings.[2] CDI represents a serious threat to patient safety,[3] and excess costs to acute care hospitals in the US are estimated to be $4.8 billion annually.[4] Antibiotics are among the most commonly prescribed medications in ICUs, and antibiotic exposure is the primary risk factor for CDI.[5-7] This is due to the intestinal dysbiosis caused by antibiotics, particularly broad-spectrum agents,[7, 8] rendering individuals more vulnerable to CDI.[7]

Antibiotic stewardship (AS) interventions are essential to reducing the burden of CDI.[9-12] The goals of AS are to enhance patient outcomes and reduce the inappropriate and over-prescribing of antibiotics.[13] An analysis of national data indicated that reducing prescription of broad-spectrum antibiotics by an estimated 30% would prevent 26% of CDI related to inpatient antibiotic use.[11] This would require only a 5% reduction of overall antibiotic use.[11]

While there is considerable literature to support the use of infection prevention interventions for reducing CDI,[14] there remain gaps about the impact and implementation of AS interventions specific to CDI. Existing research has yielded unclear and sometimes conflicting results regarding impact of AS interventions on CDI rates.[14-22] Moreover, data on patient outcomes in response to AS interventions are inconsistently defined and limited.[15, 21] For these reasons, further evaluation is needed to better understand which specific AS interventions will have the greatest impact on CDI rates.[14, 15] Potential AS strategies promising for CDI reduction

include pre-prescription authorization (PPA) and post-prescription review and feedback (PPRF).[15, 16, 22-34]

Of the antibiotic classes, FQs are one of the most frequently utilized in inpatient acute care facilities, where they are prescribed to 16.2% of patients.[35] FQ usage markedly increases the risk of CDI,[27-30, 36] and reductions in FQ use are associated with decreased HO-CDI rates in US acute care hospitals.[37] Rising CDI rates in US hospitals can in part be attributed to the FQ-resistant strain 027/BI/NAP1,[3] which accounts for the largest proportion of healthcare facility-onset CDI (HO-CDI) cases nationally (30.7%).[3]

Study outcomes and measures

The trial described in this protocol is designed to implement a FQ PPA intervention, and evaluate its implementation effectiveness and impact on CDI rates in adult medical-surgical ICU settings. This approach was chosen because restrictive AS interventions like PPA are likely to be effective, but implementation is often complex and variable between studies, making implementation evaluation difficult. We propose the integration of a FQ PPA into the electronic health record (EHR) using clinical decision support (CDS) technologies. CDS technologies have demonstrated improvements in patient outcomes in a variety of healthcare settings.[38-40] We hypothesize that this FQ PPA intervention will result in decreased CDI rates during the intervention period, and that quality improvement efforts will be enhanced by UW study-team external implementation facilitation at each site.

The primary objective is to evaluate the effectiveness of this FQ PPA intervention in reducing ICU-onset and healthcare facility-onset CDI (HO-CDI) rates in adult ICUs compared with usual care. The secondary objective is to evaluate the effectiveness of the implementation of this intervention using the Systems Engineering Initiative for Patient Safety (SEIPS) model.[42]

Methods

Study Aims and Hypothesis

The overall hypothesis of this study is that a FQ PPA intervention is an effective strategy to reduce CDI rates in the ICU setting. The primary aim of the trial is to determine the impact of FQ PPA on ICU-onset and HO-CDI rates and other clinical outcomes compared with usual care in medical-surgical adult ICUs enrolled in this trial. Consistent with Structured Taskforce of Experts Working at Reliable Standards for Stewardship (STEWARDS) Panel recommendations, we will collect ICU-onset CDI as a subset of HO-CDI rates, HO-CDI, and healthcare-associated CDI (HA-CDI) as measures of trial effects.[41] We will also collect antibiotic utilization data measured in days of therapy (DOT) per patient admission, and per patient-days, for both FQs and their most common alternatives as primary targets of the intervention.

The secondary aim of the trial is to facilitate and evaluate the implementation process, uptake, and effectiveness of the FQ PPA as a complex behavioral intervention using the SEIPS model.[42] SEIPS provides a broad and flexible way to characterize and evaluate work systems and care processes and the complex relationships among them using five work system elements: people, tools and technologies, tasks, organizational factors, and environmental factors.[56,57] This model will be used to characterize and evaluate the AS intervention and its

impact on care processes and various patient, organizational, and professional outcomes to produce a "thick" description of implementation processes[43-46] at each of the sites (described later in this article). These characteristics will then be related to clinical outcomes of the primary aim in a cross-case analysis.[44, 47]

We used the SPIRIT reporting guidelines in the preparation of this manuscript. [48]

Overall Study Design

A non-randomized stepped wedge (NR-SW) cluster design will be used, embedded within an effectiveness-implementation hybrid type 2 trial of ICUs that have elected to implement the FQ PPA.[59] This design is appropriate as it allows us to simultaneously evaluate the FQ PPA's clinical effects and the impact of the implementation approach on intervention adoption. As all ICUs were planning to implement FQ AS interventions for quality improvement practices, the NR-SW wedge design allows each site to receive the trial intervention while serving as its own control, thereby maintaining strong internal validity.

The trial will involve three phases at each ICU site. Phase One is a 3-month pre-FQ PPA preparatory period for external facilitation of the implementation, prescriber education, building the FQ PPA clinical decision support BPA, and early contextual and implementation data collection. Phase Two is the 12-month intervention period during which the FQ PPA-BPA goes live, over which time both routinely collected clinical EHR data and implementation data will be regularly collected. Phase Three is a sustainability phase during which sites develop and maintain sustainability action plans, and can choose to continue the PPA policy with no further implementation support from the trial team. This sequence will be repeated for each of the

sites until all have completed the intervention phase of the trial. Clinical variables and outcomes for the corresponding 12-month pre-intervention period will constitute the baseline for comparison with the Phase Two intervention period. The influences upon implementation and its effectiveness at each site will be assessed using a mixed-methods approach. Figure 1 provides a schematic overview of the study design and method.

Figure 1. Schematic depiction of the trial design and procedures.

Trial Organization

The Steering Committee (SC): The SC will be chaired by PI Professor Nasia Safdar, and include lead biostatistician, Professor Roger Brown, co-investigators (Dr. Pascale Carayon, Dr. Lucas Schulz, Dr. Aurora Pop-Vicas) and other study personnel (Dr. Vishala Parmasad, Dr. Alex Lepak, Michele Zimbric and Kendra Haight). The SC will meet face-to-face once before study initiation and monthly via teleconference throughout the study. The SC will be responsible for reviewing study progress and if necessary, agreeing to protocol changes to facilitate smooth running of the study.

The Data Coordinating Center (DCC): The DCC will provide expertise and support for the trial in data management, data verification, quality control and assurance, information technology for communication and trial monitoring, and statistical methods for design including statistical analyses, preparation of results in tabular and graphical formats for presentation, and publication of findings from the trial. The DCC will be located in the University of Wisconsin-

Madison, led by study biostatistician Professor Roger Brown and data manager Fauzia Osman. The UW-Madison team will be responsible for oversight of the DCC activities.

The Clinical Coordinating Center (CCC): The CCC will be responsible for overall study execution: protocol refinement, comprehensive site implementation facilitation, medical monitoring, handling of potential patient-related issues, interfacing with the DCC, and coordination with AHRQ. The CCC will be physically located at UW-Madison and led by the PI and study lead, Dr. Vishala Parmasad.

Data Collection and Management: The electronic case report forms (eCRFs) will be finalized by the DCC before being reviewed and approved by the study team. Data collected at the clinical sites will be de-identified recorded on eCRFs and entered using the clinical trial data management system. Study investigators will have access to the final trial dataset, and site personnel will have access to site-specific data.

Site Monitoring: We are planning site virtual initiation visits prior to site enrollment. In addition, we are planning to audit 10% of cases, and conduct site audits for cause or on a risk-based priority. All regulatory aspects will be monitored.

Adverse Event Monitoring: Adverse event (AE) reporting, such as side effects from alternative antibiotics or inappropriate antibiotic use, will follow established site-specific guidelines for retrospective AE monitoring and reporting. Existing research on antibiotic stewardship interventions, including FQ PPA, indicates that these types of interventions do not have adverse impacts on patient outcomes. While the antibiotics patients receive will be impacted by the FQ

PPA intervention, the alternative antibiotics available to providers all fall within best practice guidelines and the possible risks associated with these antibiotics are in equipoise with those associated with FQ. As the purpose of this study is to optimize adherence to established AS best practices, real-time adverse events monitoring was not considered necessary. Once the study is in place, an independent, ad-hoc Drug Safety and Monitoring Board (DSMB) will review a sample of charts from each study site. These charts will be extracted from the study site by site personnel and de-identified before being provided to the UW study team for review.

Patient and Public Involvement

The UW Team has consistently worked with a patient stakeholder group, The Patients Engaged in Education and Research (PEER) Group, soliciting feedback regarding patient priorities in healthcare associated infection prevention. The overall goals of this study are in line with expressed patient priorities of improving antibiotic stewardship and decreasing CDI, however this study specifically targets the prescribing practice of ICU providers. Patients were thus not involved in the design, recruitment, conduct, or assessment of the study. The results of this study will be disseminated back to patient stakeholders through venues such as meetings, patient-provider conferences, and working with the Madison Patient Education Resource Center.

Study Population, inclusion and exclusion criteria

Adult general medical and surgical ICU sites are the targets of this trial. Participant sites must have a pre-existing AS program with pharmacist and infectious disease (ID) physician support and their EHR vendor as Epic Systems Corporation. Their EHR must have the ability to extract antibiotic usage data (days of therapy), required outcome data (CDI, mortality, length of ICU stay), and data on indications for antibiotic use. They must additionally be adherent to best practices for infection control relevant to CDI. Sites are considered ineligible to participate if they are already restricting FQ or another antibiotic associated with CDI risk. These criteria were selected so that the intervention could be implemented in a standardized manner. The use of Epic Systems Corporation as an EHR vendor was necessary to ensure the changes necessary to the EHR will be feasible at each site. The UW study team will provide templates for and information technology consultations on the required EHR changes and data extraction processes.

Once initiated, the intervention will be applied to all patients admitted to the ICU and all healthcare workers involved in antibiotic prescribing in that ICU. The intervention and usual care strategies will be allocated at the ICU level, thus inclusion and exclusion criteria apply to ICUs, not to individual patients. Assigning ICUs rather than individuals to the intervention is appropriate given horizontal transmission of *C. difficile.*

Recruitment and Consent

We chose a total of 12 ICUS to participate in the trial to ensure a patient sample size large enough to detect clinically meaningful and statistically significant differences in CDI outcomes between the intervention and usual care, and to account for site attrition. Recruitment emails will be sent out via regional and national research networks, pharmacist networks, and AS networks. Informed consent will be obtained by study lead from all personnel participating in interviews and surveys about implementation, and collected data will be de-identified before inclusion in the study. Recruitment will take place on a rolling basis to account for variations in time to completion of pre-trial regulatory activities.

Study Intervention

This multicomponent study constitutes a suite of resources for the introduction and assessment of FQ prescribing best practices in adult ICUs, via a FQ PPA structured around a CDS system within site EHRs. The trial team supports the implementation process at each site and facilitates the development of site-specific CDS FQ PPA protocols.

The FQ PPA CDS intervention constitutes a best practices alert (BPA) that appears when providers attempt to prescribe FQs in the ICU. The BPA informs providers that FQ use is restricted, and provides links to select alternative antibiotics. Providers can alternatively contact a designated member of the hospital AS team to discuss the choice of drug via the BPA. The BPA and order set will be constructed to allow tracking of non-adherence to the FQ PPA policy, allowing the measurement of fidelity to the intervention. FQs will be discontinued on patients who are already on a FQ when they are transferred to the ICU.

Before and during the implementation of the FQ PPA policy at each site, the trial team will engage in the external implementation facilitation of this intervention, through supportive activities consistent with evidence-based implementation principles[49-50] (Table 1). This approach was purposefully developed by examining relevant implementation literature.[51-54]

Table 1. Evidence-based Implementation Principles

Implementation principles	What will be done at each site
Top management commitment	Immediately prior to initiating the PPA, we will ask each site's leadership to communicate support for the intervention. Depending on the site, this could include the board of directors, medical staff boards of governance, ICU leadership, the ICUs' quality improvement committee, and/or the pharmacy and therapeutics team.
User participation	After we identify site coordinators, we will ask them to identify the attendings, fellows, residents, advanced practice providers, pharmacists, and ID staff from the AS team who will be impacted by the PPA.
Communication and feedback	We will set up conference calls with these providers to identify champions, and ask them to describe any barriers to and facilitators of implementing the PPA. Individuals identified as possible champions and opinion leaders will be contacted. We will engage them to identify ways they might promote the intervention throughout the trial.
Training	We will set up conference calls via webinar with relevant providers in order to provide training. We will have separate coaching sessions with the unit pharmacists and the AS team to handle calls/questions from providers regarding FQ prescribing. We will also distribute a toolkit to providers that will include a summary of research supporting FQ PPA, data on their ICU's CDI and FQ usage rates, a FQ alternative antibiotics card, a cross-table antibiogram and links to relevant prescribing guides and decision support tools.
Learning	Once these activities have been completed, we will closely analyze the barriers and facilitators at each site and work with site coordinators to address the barriers and leverage facilitators to the greatest extent possible. Once the PPA policy has been initiated at each site we will continue to provide support to aid the implementation of the PPA

	policy. We will also hold monthly phone calls with the site coordinators to discuss how any emerging barriers can be addressed while maintaining fidelity.
Project management	We will identify coordinators at each site who will act as the primary contact for the trial. We will work with the coordinators to identify barriers and facilitators for the implementation of the PPA policy at their sites. We will also ask the coordinators to identify staff who seem enthusiastic about the intervention that may act as champions at their site.

Usual care

Usual care for this trial will include no active restriction of FQ use. Sites may still choose to use post prescription feedback for FQ if that is their usual practice. There may be restriction of other antibiotics as per a site's usual practice and an active AS program must be in place. Given expected variation in usual practice, we will collect data on usual AS and infection prevention practices at each site to understand the spectrum of usual care.

Data Collection and Analysis

Aim 1: Data Collection

For the primary aim, data will be extracted from each site's Clarity database derived from the PennChart (Epic) EHR application. The trial team will provide each site with a standardized data extraction manual and Microsoft SQL coding-logic document delineating the required data variables. Routinely collected patient-level clinically generated data will be

extracted for the 12-month Phase Two intervention period, and the corresponding 12-month pre-intervention period.

We will collect incidence of HO-CDI, location-specific ICU-onset CDI, and HA-CDI. In order to more closely associate the effects on CDI rates with a site's antibiotic use, the fidelity of the intervention will be confirmed by measuring FQ and other antibiotic usage in DOT per patient admission and DOT per 1000 patient-days. To evaluate both the positive and negative clinical outcomes of this intervention to participating ICUs, mortality, readmissions, hospital length of stay, and the incidence of other (non-CDI) HAIs will also be assessed. Table 2 shows the data variables that will be collected. The de-identified clinical data will be sent to the trial team via a personal health information secure website for statistical analysis.

Table 2. Variables to be collected for Aim 1 analysis

Unit (or hospital)-level variables	Type of variable	Operational Definition	How extracted
Healthcare facility-onset CDI (HO-CDI) with ICU-onset	Primary outcome	Positive test for CDI from ICU specimen sent from symptomatic patient, on or after day 4 of admission to healthcare facility [63]	Routinely collected by infection control
Healthcare facility-onset CDI (HO-CDI)	Primary outcome	Positive test for CDI from symptomatic patient on or after day 4 of admission to healthcare facility.[63]	Routinely collected by infection control
Healthcare-associated CDI (HA-CDI)	Primary outcome	Positive test for CDI from a symptomatic patient who was discharged from the facility ≤ 4 weeks prior to date of stool specimen collection[63]	Routinely collected by infection control

FQ usage	Secondary outcome	Days of therapy (DOT) per patient admission and DOT per 1000 Patient-Days (PD)[a]	EHR-routinely collected by antibiotic stewardship
Other antibiotic usage	Secondary outcome	DOT per patient admission and DOT per 1000 PD[a]	EHR-routinely collected by antibiotic stewardship
AKI	Secondary outcome	Kidney Disease Improving Global Outcomes (KDIGO) guideline definition[64, b]	EHR via chart review
Mortality	Secondary outcome	Hospital mortality	Administrative data
Length of stay	Secondary outcome	Duration of stay in the hospital	Administrative data
Readmissions	Secondary outcome	Within 30 post discharge	Administrative data
Other HAIs (central line-associated bloodstream infection)	Secondary outcome	During ICU or hospital stay	Routinely collected by infection control
Infection control interventions	Descriptive	Compliance with environmental cleaning, hand hygiene and contact precautions	Routinely collected by infection control with direct observations
Patient level variables			
Age	Descriptive	Years	Extracted from EHR
Sex	Descriptive	Male; Female; Unknown/Not provided	Extracted from EHR
Race	Descriptive	American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White[c]	Extracted from EHR
Ethnicity	Descriptive	Hispanic or Latino; Not Hispanic or Latino[c]	Extracted from EHR

Comorbidity and severity score	Descriptive	Charlson Comorbidity Index score[65, 66] and APACHE score[67, 68]	Extracted from EHR
Number of prior CDI	Descriptive	Number of prior cases of healthcare-associated CDI, confirmed by positive test	Extracted from EHR
Appropriateness of antibiotic use	Secondary outcome	Use is concordant with institutional guidelines as judged by 2 AS team members at each site.[69] A physician from the investigative team (NS) will adjudicate disagreements.[d]	Chart review of a sample of cases

[a] A single DOT will be recorded for each individual antibiotic administered to a patient on a given day. Antibiotic use will be normalized to patient days of therapy per 1000 patient-days (PD) as well as per patient admission.

[b] The KDIGO guideline defines AKI as any of the following: Increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or Increase in serum creatinine to ≤ 1.5 times baseline or urine volume < 0.5 mg/kg/hour for 6 hours[64]

[c] These categories are consistent with the US Office of Management and Budget minimum standards for maintaining, collecting, and presenting race and ethnicity for all grant projects defined in OMB Directive No. 15. The National Institutes of Health Grants Policy Statement supports the use of these categories.[70]

[d] The following published guidance will be used to judge appropriateness: the Hopkins "Four Moments in Antibiotic Decision-Making" approach: (1) Was antibiotic therapy indicated based on known clinical, microbiological, radiographic, and severity of illness findings of the patient? (2) Was the most appropriate empiric antibiotic regimen selected? (3) Was therapy appropriately adjusted or stopped after a reassessment by day 3 of antibiotics? (4) Was the duration of therapy appropriate for the infection being treated?[71] Given the intensive resources required for this endeavor, we will focus on sepsis treatment.

Aim 1: Statistical Analysis

Using 10.5 per 10,000 patient day CDI rate as the base value, reducing it by 50% based on the literature, and using a NR-SW cluster design, we will need monthly assessments, 12 months pre- and 12 months post-intervention, assuming 10 beds per ICU, in 6 ICUs to achieve power at around 0.80, with two-tailed alpha test at 0.05. We have selected a far more

conservative sample size of 12 ICUs to detect an effect of less than 50% which may nevertheless be clinically meaningful, also allowing for ICU attrition. Simulation studies[55] have indicated that adequate power to detect effects in balanced data series, as few as 12 data points, may be reasonable for our regression discontinuity analysis in detecting program intervention level and trend change.

We will use two analytic strategies, the first being a multilevel logit random effects model on the incidence of CDI of all ICUs sites, following procedures suggested by the Huynh, et al (2016) simulation for analysis of NR-SW designs.[56] All models will be constructed using MLwiN software Version 3.02.[57]

The second analytic approach will be to use interrupted time series analysis[58] for step-by-step CDI rates per ICU, using the 12 month pre- and 12 month post-intervention data. In this design, data are collected at multiple instances over time before and after an intervention is introduced to detect whether the intervention has an effect significantly greater than the underlying secular trend. Since we anticipate an abrupt and permanent change in the outcome after implementation of the intervention program, we propose regression discontinuity analysis using an autoregressive regression model. All interrupted time series models will be constructed using Stata's Version 14 routine interrupted time series analysis.[59]

Aim 2: Data Collection

Data collection for the implementation evaluation and analysis will occur during Phases One and Two, simultaneous with intervention launch. Data sources will include (1) aggregated site contextual data (2) implementation process documentation, and (3) study feedback from site participants, using IRB-approved surveys, semi-structured interview and focus group prompts, and informed consent will be obtained from all participants. See Table 3 for a summary of data sources and study outcomes for the secondary aim.

Table 3. Implementation data sources and analysis

Domain	Instrument	Components	Outcome measures
Contextual site information	Site infection prevention practices	Infection prevention program, personnel and infrastructure; infection prevention and control activities; risk assessment; frequency of updates; educational outreach; active surveillance screening and procedure by organism; screening procedure for HAIs; pre-surgical decolonization procedures and surgical targets; contact precautions by organism; hand hygiene procedures, compliance and feedback; personal protective equipment (PPE) use; environmental cleaning procedures; surveillance reporting	Contextual information for: cross-site comparison; implementation analysis
	Site antibiotic stewardship practices	AS leadership support and infrastructure; AS educational updates; antibiotic indication documentation procedures; facility-specific treatment recommendations and monitoring; antibiotic time out precedures; pre-prescription program procedures; audit and	Contextual information for: cross-site comparison; implementation analysis

		feedback specifications and process; antibiotic utilization monitoring; antibiotic consumption monitoring and reports; antibiotic susceptibility testing; antibiogram data;	
	ICU information	ICU facility type and model; number of beds; ICU critical statistics (avg. length of stay, number of patients per year; patient days per year or month); ICU personnel information; ICU prescriber data; AS (pharmacist and infectious disease physician) support for ICU prescribers;	Contextual information for: cross-site comparison; implementation analysis
Implementation practices	Implementation diary	Timeline of pre- and post-implementation related activities, participants, and durations	Implementation analysis: timeline
	Site Startup Activities	Identification of site contacts and implementation roles; pre-intervention support and task status	Implementation analysis: timeline
	Check-in meeting notes	Record of changes to sites AS or IP practices; barriers and facilitators to introducing intervention	Implementation analysis: barriers and facilitators
	Usability test	Pre-launch feedback on BPA from primary ICU prescribers, performed in the playground environment of the EHR	Implementation analysis: integration into work systems; support
Intervention assessment	Surveys	Acceptance of BPA; complexity; ease of use; need for technical support; integration into EHR; consistency; confidence about use;	Implementation analysis
	Semi-structured interviews with BPA users and AS support personnel	Pluses and minuses of intervention implementation (notification, training/education, release), role in implementation; effect of BPA integration into work system and workflow (positives/negatives); effect of BPA on workload, teamwork, changes	Implementation analysis
	Focus groups	ICU healthcare providers grouped by specialty discuss their experiences of the FQ PPA intervention focusing on pluses and minuses of the implementation process	Implementation analysis

Aim 2: Implementation Analysis

The secondary outcome measures of this intervention include evaluating the effectiveness of the implementation processes at each site using the SEIPS conceptual framework. A multiple case study design[43, 44, 60] with a mixed methods approach[42, 45, 46] will be used to evaluate the implementation process, with each participating ICU constituting a single site. The SEIPS framework will be used to relate these characteristics to the effectiveness outcomes at each site in a cross-case analysis (Figure 2).

Figure 2. Systems Engineering Initiative for Patient Safety (SEIPS) Framework - Fluoroquinolone PPA Implementation in Acute Care Settings.

The concurrent implementation of the FQ intervention and evaluation of its impact and corresponds to the convergent parallel trial design in mixed methods research[45, 46, 61] in which quantitative and qualitative data are collected simultaneously. The final outcome of this analysis will be a "thick" description of implementation with varying levels of success as measured by the primary outcomes. "Thick" description refers to the use of qualitative methods that provide depth of understanding of both process and the inner and outer contexts of intervention implementation, to complement the breadth of understanding allowed by quantitative analysis of clinical data.[61] Site-specific data will be combined in a cross-case analysis table in an Excel spreadsheet, in an adaptation of the predictor-outcome-consequences matrix of Miles and Huberman.[47] We will use a systematic comparative pattern analysis method to iteratively compare and emphasize the combination of potential contributing factors that function together as a system.[60] This is an important feature of the analysis that fits with the systems approach, which is at the core of the SEIPS model.[42] Analysis of the compiled data will be performed by a team of researchers with varied expertise in implementation science, human factors and systems engineering, and infectious disease. The triangulation with multiple analysts will enhance the quality of the analysis and ensure its rigor. [61,62]

Discussion

We expect this study to demonstrate that the FQ PPA intervention has resulted in decreases in FQ usage in ICU settings, and lowered ICU-onset and HO-onset CDI rates. We also expect to have collected rich data on implementation to guide future FQ PPA interventions, including important information on barriers and strategies to overcome them.

At the project conclusion, we will have (1) assessed the effects on CDI rates of the FQ PPA implementation-intervention trial and (2) evaluated the most effective implementation processes for introducing this FQ PPA in ICU settings. The knowledge from this project could benefit subsequent projects focused on instituting FQ PPA in acute care settings, and improve the quality of AS programs nationally. The integration of the FQ PPA into CDS technologies with real-time clinical expertise availability has the potential to improve the quality of antibiotic prescribing throughout entire hospital systems as well. Given the complexity of this intervention, the findings may not be applicable to the implementation of simpler FQ PPA efforts. However, there are critical gaps in the knowledge of how to best target CDI with AS interventions, which this study will address.

The evolving COVID-19 pandemic of 2020 is likely to affect site recruitment and results for this trial. Amongst other effects, prescribing practices for patients with suspected or confirmed COVID-19 infection in the ICU may influence antibiotic use. We will attempt to address this by comparing site prescribing practices pre -COVID-19 and post-COVID-19.

Ethics and dissemination

Ethical approval for this study was obtained from the University of Wisconsin-Madison Health Sciences Institutional Review Board (Protocol Version: 2018-0852-CP015). Individual sites may choose to undergo their own internal review process or cede to the IRB of the University of Wisconsin. The study protocol was approved on July 24, 2018 and this manuscript reports on the most updated version of the protocol approved on October 19, 2020. All participant sites will be informed prior to enrollment that participation is completely voluntary, that they can withdraw from participation at any time, and that their decision to participate or not will not affect their health care in any way.

Upon completion of the study, we will present the results at major scientific conferences and will publish the results in peer-reviewed journals.

Author contributions

NS, PC, RB, AL, and LS conceived of the study concept and design. VP drafted the overall protocol, with critical input from NS and RB for study design, recruitment, and statistical analysis. RB drafted protocol sections for statistical analyses; and PC for implementation analysis. All authors provided critical feedback and approved the final version of the manuscript.

Competing Interests

None declared.

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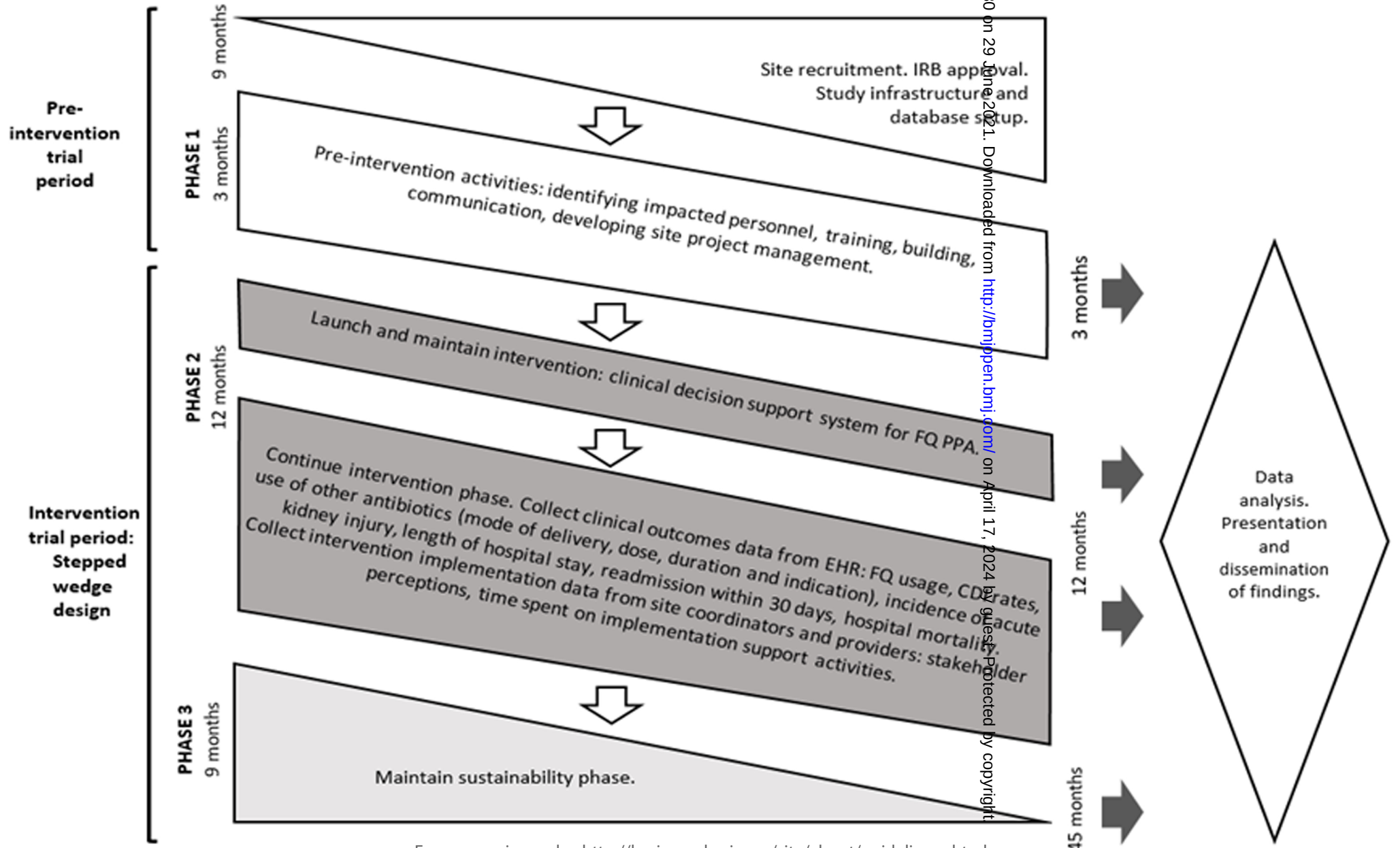

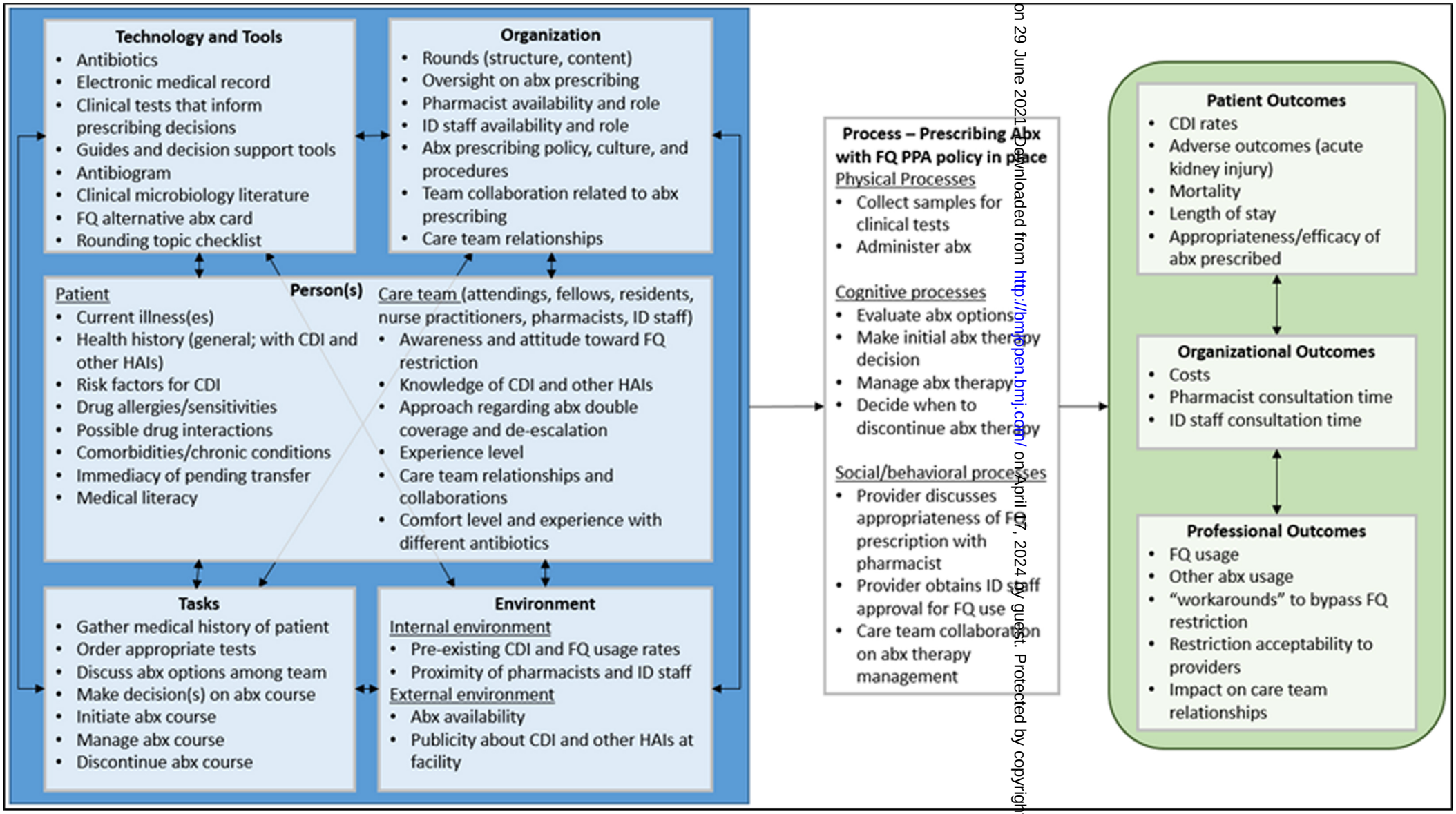

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	NCT03848689 at clinicaltrials.gov
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	23
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	10

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg,	6-7

		systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	19
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection,			

management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-24
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	26
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	26
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	26
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	26

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Notes:

- 2a: NCT03848689 at clinicaltrials.gov The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 30. October 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

A study protocol for decreasing ICU-associated Clostridioides difficile infection through fluoroquinolone restriction: The FIRST trial

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Manuscript ID	bmjopen-2020-046480.R1
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A study protocol for decreasing ICU-associated *Clostridioides difficile* infection through fluoroquinolone restriction: The FIRST trial

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Abstract

Introduction: Clostridioides difficile infection (CDI) is the one of the most common healthcare-associated infection (HAI) in the USA, having high incidence in intensive care units (ICU). Antibiotic use increases CDI risk, with fluoroquinolones (FQ) particularly implicated. In healthcare settings, antibiotic stewardship (AS) and infection control interventions are effective for CDI control, but there is little evidence regarding the most effective AS interventions. Pre-prescription authorization (PPA) restricting FQs is a potentially promising AS intervention to reduce CDI. This study will evaluate the effectiveness of a FQ PPA intervention in reducing CDI rates in adult ICUs compared with pre-intervention care, and evaluate implementation effectiveness using a human-factors and systems engineering model.

Methods and analysis: This is a multisite stepped-wedge cluster effectiveness-implementation clinical trial. The trial will take place in 12 adult medical-surgical ICUs with ≥10 beds, Epic as electronic health record (EHR), and preexisting AS programs. Sites will receive facilitated implementation support over the 15-month trial period, succeeded by 9 months follow-up. The intervention comprises a clinical decision support system for FQ PPA, integrated into site EHRs. Each ICU will be considered a single site, and all ICU admissions included in analysis. Clinical data will be extracted from EHRs throughout the trial and compared to the corresponding pre-trial period, which will constitute the baseline for statistical analysis. Outcomes will include ICU-onset CDI rates, FQ days of therapy (DOT), alternative antibiotic DOT, average length of stay,

and hospital mortality. The study team will also collect implementation data to assess implementation effectiveness using the Systems Engineering Initiative for Patient Safety model.

Ethics and dissemination: The trial was approved by the Institutional Review Board at the University of Wisconsin-Madison (2018-0852-CP015). Results will be made available to participating sites, funders, infectious disease societies, critical care societies, and other researchers.

Trial registration: NCT03848689; Pre-results.

Article Summary

Strengths and limitations of this study

- FIRST will provide one of the few national, multi-site, comprehensive studies that investigate the effect on intensive care unit-associated-CDI of fluoroquinolone pre-prescription authorization integrated as a computerized decision support tool.
- Our trial design will allow us to look at changes in outcome measures over time at the same site, delineating a temporal sequence to ICU-associated and hospital associated CDI, providing more evidence for causality.

- Our approach simultaneously introduces antibiotic stewardship FQ prescribing best-practices, and assesses the introduction of these practices, facilitating continuous implementation improvement.
- The primary limitation to this trial is a slow-down in recruitment rates with the SARS-coV-2 Covid-19 pandemic, and the uncertain effects of this pandemic upon current ICU sites.

Keywords: Hospital associated *Clostridiodes difficile* infection, antibiotic stewardship, fluoroquinolone restriction, pre-prescription authorization, implementation effectiveness

Introduction

Background and rationale

Clostridioides difficile infection (CDI) is the most prevalent healthcare-associated infection in the United States[1] and CDI rates are consistently higher in intensive care unit (ICU) settings.[2] CDI represents a serious threat to patient safety,[3] and excess costs to acute care hospitals in the US are estimated to be $4.8 billion annually.[4] Antibiotics are among the most commonly prescribed medications in ICUs, and antibiotic exposure is the primary risk factor for CDI.[5-7] This is due to the intestinal dysbiosis caused by antibiotics, particularly broad-spectrum agents,[7, 8] rendering individuals more vulnerable to CDI.[7]

Antibiotic stewardship (AS) interventions are essential to reducing the burden of CDI.[9-12] The goals of AS are to enhance patient outcomes and reduce the inappropriate and over-prescribing of antibiotics.[13] An analysis of national data indicated that reducing prescription of

broad-spectrum antibiotics by an estimated 30% would prevent 26% of CDI related to inpatient antibiotic use.[11] This would require only a 5% reduction of overall antibiotic use.[11]

While there is considerable literature to support the use of infection prevention interventions for reducing CDI,[14] there remain gaps about the impact and implementation of AS interventions specific to CDI. Existing research has yielded unclear and sometimes conflicting results regarding impact of AS interventions on CDI rates.[14-22] Moreover, data on patient outcomes in response to AS interventions are inconsistently defined and limited.[15, 21] For these reasons, further evaluation is needed to better understand which specific AS interventions will have the greatest impact on CDI rates.[14, 15] Potential AS strategies promising for CDI reduction include pre-prescription authorization (PPA) and post-prescription review and feedback (PPRF).[15, 16, 22-34]

Of the antibiotic classes, FQs are one of the most frequently utilized in inpatient acute care facilities, where they are prescribed to 16.2% of patients.[35] FQ usage markedly increases the risk of CDI,[27-30, 36] and reductions in FQ use are associated with decreased HO-CDI rates in US acute care hospitals.[37] Rising CDI rates in US hospitals can in part be attributed to the FQ-resistant strain 027/BI/NAP1,[3] which accounts for the largest proportion of healthcare facility-onset CDI (HO-CDI) cases nationally (30.7%).[3]

Study outcomes and measures

The trial described in this protocol is designed to implement a FQ PPA intervention, and evaluate its implementation effectiveness and impact on CDI rates in adult medical-surgical ICU

settings. This approach was chosen because restrictive AS interventions like PPA are likely to be effective, but implementation is often complex and variable between studies, making implementation evaluation difficult. We propose the integration of a FQ PPA into the electronic health record (EHR) using clinical decision support (CDS) technologies. CDS technologies have demonstrated improvements in patient outcomes in a variety of healthcare settings.[38-40] We hypothesize that this FQ PPA intervention will result in decreased CDI rates during the intervention period, and that quality improvement efforts will be enhanced by UW study-team external implementation facilitation at each site.

The primary objective is to evaluate the effectiveness of this FQ PPA intervention in reducing ICU-onset and healthcare facility-onset CDI (HO-CDI) rates in adult ICUs compared with usual care. The secondary objective is to evaluate the effectiveness of the implementation of this intervention using the Systems Engineering Initiative for Patient Safety (SEIPS) model.[41]

Methods

Study Aims and Hypothesis

The overall hypothesis of this study is that a FQ PPA intervention is an effective strategy to reduce CDI rates in the ICU setting. The primary aim of the trial is to determine the impact of FQ PPA on ICU-onset and HO-CDI rates and other clinical outcomes compared with usual care in medical-surgical adult ICUs enrolled in this trial. Consistent with Structured Taskforce of Experts Working at Reliable Standards for Stewardship (STEWARDS) Panel recommendations, we will collect ICU-onset CDI as a subset of HO-CDI rates, HO-CDI, and healthcare-associated CDI (HA-CDI) as measures of trial effects.[42] We will also collect antibiotic utilization data measured in

days of therapy (DOT) per patient admission, and per patient-days, for both FQs and their most common alternatives as primary targets of the intervention.

The secondary aim of the trial is to facilitate and evaluate the implementation process, uptake, and effectiveness of the FQ PPA as a complex behavioral intervention using the SEIPS model.[41] SEIPS provides a broad and flexible way to characterize and evaluate work systems and care processes and the complex relationships among them using five work system elements: people, tools and technologies, tasks, organizational factors, and environmental factors.[43] This model will be used to characterize and evaluate the AS intervention and its impact on care processes and various patient, organizational, and professional outcomes to produce a "thick" description of implementation processes[44-47] at each of the sites (described later in this article). These characteristics will then be related to clinical outcomes of the primary aim in a cross-case analysis.[45, 48]

We used the SPIRIT reporting guidelines in the preparation of this manuscript.[49]

Overall Study Design

A non-randomized stepped wedge (NR-SW) cluster design will be used, embedded within an effectiveness-implementation hybrid type 2 trial of ICUs that have elected to implement the FQ PPA.[50] This design is appropriate as it allows us to simultaneously evaluate the FQ PPA's clinical effects and the impact of the implementation approach on intervention adoption. As all ICUs were planning to implement FQ AS interventions for quality improvement practices, the NR-SW wedge design allows each site to receive the trial intervention while serving as its own control, thereby maintaining strong internal validity.

The trial will involve three phases at each ICU site. Phase One is a 3-month pre-FQ PPA preparatory period for external facilitation of the implementation, prescriber education, building the FQ PPA clinical decision support BPA, and early contextual and implementation data collection. Phase Two is the 12-month intervention period during which the FQ PPA-BPA goes live, over which time both routinely collected clinical EHR data and implementation data will be regularly collected. Phase Three is a sustainability phase during which sites develop and maintain sustainability action plans, and can choose to continue the PPA policy with no further implementation support from the trial team. This sequence will be repeated for each of the sites until all have completed the intervention phase of the trial. Clinical variables and outcomes for the corresponding 12-month pre-intervention period will constitute the baseline for comparison with the Phase Two intervention period. The influences upon implementation and its effectiveness at each site will be assessed using a mixed-methods approach. Figure 1 provides a schematic overview of the study design and method.

Figure 1. Schematic depiction of the trial design and procedures.

Trial Organization

The Steering Committee (SC): The SC will be chaired by PI Professor Nasia Safdar, and include lead biostatistician, Professor Roger Brown, co-investigators (Dr. Pascale Carayon, Dr. Lucas Schulz, Dr. Aurora Pop-Vicas) and other study personnel (Dr. Vishala Parmasad, Dr. Alex Lepak, Michele Zimbric and Kendra Haight). The SC will meet face-to-face once before study initiation and monthly via teleconference throughout the study. The SC will be responsible for reviewing

study progress and if necessary, agreeing to protocol changes to facilitate smooth running of the study.

The Data Coordinating Center (DCC): The DCC will provide expertise and support for the trial in data management, data verification, quality control and assurance, information technology for communication and trial monitoring, and statistical methods for design including statistical analyses, preparation of results in tabular and graphical formats for presentation, and publication of findings from the trial. The DCC will be located in the University of Wisconsin-Madison, led by study biostatistician Professor Roger Brown and data manager Fauzia Osman. The UW-Madison team will be responsible for oversight of the DCC activities.

The Clinical Coordinating Center (CCC): The CCC will be responsible for overall study execution: protocol refinement, comprehensive site implementation facilitation, medical monitoring, handling of potential patient-related issues, interfacing with the DCC, and coordination with AHRQ. The CCC will be physically located at UW-Madison and led by the PI and study lead, Dr. Vishala Parmasad.

Data Collection and Management: The electronic case report forms (eCRFs) will be finalized by the DCC before being reviewed and approved by the study team. Data collected at the clinical sites will be de-identified recorded on eCRFs and entered using the clinical trial data management system. Study investigators will have access to the final trial dataset, and site personnel will have access to site-specific data.

Site Monitoring: We are planning site virtual initiation visits prior to site enrollment. In addition, we are planning to audit 10% of cases, and conduct site audits for cause or on a risk-based priority. All regulatory aspects will be monitored.

Adverse Event Monitoring: Adverse event (AE) reporting, such as side effects from alternative antibiotics or inappropriate antibiotic use, will follow established site-specific guidelines for retrospective AE monitoring and reporting. Existing research on antibiotic stewardship interventions, including FQ PPA, indicates that these types of interventions do not have adverse impacts on patient outcomes. While the antibiotics patients receive will be impacted by the FQ PPA intervention, the alternative antibiotics available to providers all fall within best practice guidelines and the possible risks associated with these antibiotics are in equipoise with those associated with FQ. As the purpose of this study is to optimize adherence to established AS best practices, real-time adverse events monitoring was not considered necessary. Once the study is in place, an independent, ad-hoc Drug Safety and Monitoring Board (DSMB) will review a sample of charts from each study site. These charts will be extracted from the study site by site personnel and de-identified before being provided to the UW study team for review.

Patient and Public Involvement

The UW Team has consistently worked with a patient stakeholder group, The Patients Engaged in Education and Research (PEER) Group, soliciting feedback regarding patient priorities in healthcare associated infection prevention. The overall goals of this study are in line with

expressed patient priorities of improving antibiotic stewardship and decreasing CDI, however this study specifically targets the prescribing practice of ICU providers. Patients were thus not involved in the design, recruitment, conduct, or assessment of the study. The results of this study will be disseminated back to patient stakeholders through venues such as meetings, patient-provider conferences, and working with the Madison Patient Education Resource Center.

Study Population, inclusion and exclusion criteria

Adult general medical and surgical ICU sites are the targets of this trial. Participant sites must have a pre-existing AS program with pharmacist and infectious disease (ID) physician support and their EHR vendor as Epic Systems Corporation. Their EHR must have the ability to extract antibiotic usage data (days of therapy), required outcome data (CDI, mortality, length of ICU stay), and data on indications for antibiotic use. They must additionally be adherent to best practices for infection control relevant to CDI. Sites are considered ineligible to participate if they are already restricting FQ or another antibiotic associated with CDI risk. These criteria were selected so that the intervention could be implemented in a standardized manner. The use of Epic Systems Corporation as an EHR vendor was necessary to ensure the changes necessary to the EHR will be feasible at each site. The UW study team will provide templates for

and information technology consultations on the required EHR changes and data extraction processes.

Once initiated, the intervention will be applied to all patients admitted to the ICU and all healthcare workers involved in antibiotic prescribing in that ICU. The intervention and usual care strategies will be allocated at the ICU level, thus inclusion and exclusion criteria apply to ICUs, not to individual patients. Assigning ICUs rather than individuals to the intervention is appropriate given horizontal transmission of *C. difficile.*

Recruitment and Consent

We chose a total of 12 ICUS to participate in the trial to ensure a patient sample size large enough to detect clinically meaningful and statistically significant differences in CDI outcomes between the intervention and usual care, and to account for site attrition. Recruitment emails will be sent out via regional and national research networks, pharmacist networks, and AS networks. Informed consent will be obtained by study lead from all personnel participating in interviews and surveys about implementation, and collected data will be de-identified before inclusion in the study. Recruitment will take place on a rolling basis to account for variations in time to completion of pre-trial regulatory activities.

Study Intervention

This multicomponent study constitutes a suite of resources for the introduction and assessment of FQ prescribing best practices in adult ICUs, via a FQ PPA structured around a

CDS system within site EHRs. The trial team supports the implementation process at each site and facilitates the development of site-specific CDS FQ PPA protocols.

The FQ PPA CDS intervention constitutes a best practices alert (BPA) that appears when providers attempt to prescribe FQs in the ICU. The BPA informs providers that FQ use is restricted, and provides links to select alternative antibiotics. Providers can alternatively contact a designated member of the hospital AS team to discuss the choice of drug via the BPA. The BPA and order set will be constructed to allow tracking of non-adherence to the FQ PPA policy, allowing the measurement of fidelity to the intervention. FQs will be discontinued on patients who are already on a FQ when they are transferred to the ICU.

Before and during the implementation of the FQ PPA policy at each site, the trial team will engage in the external implementation facilitation of this intervention, through supportive activities consistent with evidence-based implementation principles (Table 1).[51, 52] This approach was purposefully developed by examining relevant implementation literature.[52-55]

Table 1. Evidence-based Implementation Principles

Implementation principles	What will be done at each site
Top management commitment	Immediately prior to initiating the PPA, we will ask each site's leadership to communicate support for the intervention. Depending on the site, this could include the board of directors, medical staff boards of governance, ICU leadership, the ICUs' quality improvement committee, and/or the pharmacy and therapeutics team.
User participation	After we identify site coordinators, we will ask them to identify the attendings, fellows, residents, advanced practice providers, pharmacists, and ID staff from the AS team who will be impacted by the PPA.

Communication and feedback	We will set up conference calls with these providers to identify champions, and ask them to describe any barriers to and facilitators of implementing the PPA. Individuals identified as possible champions and opinion leaders will be contacted. We will engage them to identify ways they might promote the intervention throughout the trial.
Training	We will set up conference calls via webinar with relevant providers in order to provide training. We will have separate coaching sessions with the unit pharmacists and the AS team to handle calls/questions from providers regarding FQ prescribing. We will also distribute a toolkit to providers that will include a summary of research supporting FQ PPA, data on their ICU's CDI and FQ usage rates, a FQ alternative antibiotics card, a cross-table antibiogram and links to relevant prescribing guides and decision support tools.
Learning	Once these activities have been completed, we will closely analyze the barriers and facilitators at each site and work with site coordinators to address the barriers and leverage facilitators to the greatest extent possible. Once the PPA policy has been initiated at each site we will continue to provide support to aid the implementation of the PPA policy. We will also hold monthly phone calls with the site coordinators to discuss how any emerging barriers can be addressed while maintaining fidelity.
Project management	We will identify coordinators at each site who will act as the primary contact for the trial. We will work with the coordinators to identify barriers and facilitators for the implementation of the PPA policy at their sites. We will also ask the coordinators to identify staff who seem enthusiastic about the intervention that may act as champions at their site.

Usual care

Usual care for this trial will include no active restriction of FQ use. Sites may still choose to use post prescription feedback for FQ if that is their usual practice. There may be restriction of other antibiotics as per a site's usual practice and an active AS program must be in place. Given expected variation in usual practice, we will collect data on usual AS and infection prevention practices at each site to understand the spectrum of usual care.

Data Collection and Analysis

Aim 1: Data Collection

For the primary aim, data will be extracted from each site's Clarity database derived from the PennChart (Epic) EHR application. The trial team will provide each site with a standardized data extraction manual and Microsoft SQL coding-logic document delineating the required data variables. Routinely collected patient-level clinically generated data will be extracted for the 12-month Phase Two intervention period, and the corresponding 12-month pre-intervention period.

We will collect incidence of HO-CDI, location-specific ICU-onset CDI, and HA-CDI. In order to more closely associate the effects on CDI rates with a site's antibiotic use, the fidelity of the intervention will be confirmed by measuring FQ and other antibiotic usage in DOT per patient admission and DOT per 1000 patient-days. To evaluate both the positive and negative clinical outcomes of this intervention to participating ICUs, mortality, readmissions, hospital length of stay, and the incidence of other (non-CDI) HAIs will also be assessed. Table 2 shows the data variables that will be collected. The de-identified clinical data will be sent to the trial team via a personal health information secure website for statistical analysis.

Table 2. Variables to be collected for Aim 1 analysis

Unit (or hospital)-level variables	Type of variable	Operational Definition	How extracted

Healthcare facility-onset CDI (HO-CDI) with ICU-onset	Primary outcome	Positive test for CDI from ICU specimen sent from symptomatic patient, on or after day 4 of admission to healthcare facility [56]	Routinely collected by infection control
Healthcare facility-onset CDI (HO-CDI)	Primary outcome	Positive test for CDI from symptomatic patient on or after day 4 of admission to healthcare facility.[56]	Routinely collected by infection control
Healthcare-associated CDI (HA-CDI)	Primary outcome	Positive test for CDI from a symptomatic patient who was discharged from the facility ≤ 4 weeks prior to date of stool specimen collection[56]	Routinely collected by infection control
FQ usage	Secondary outcome	Days of therapy (DOT) per patient admission and DOT per 1000 Patient-Days (PD)[a]	EHR-routinely collected by antibiotic stewardship
All other antibiotic usage	Secondary outcome	DOT per patient admission and DOT per 1000 PD[a]	EHR-routinely collected by antibiotic stewardship
AKI	Secondary outcome	Kidney Disease Improving Global Outcomes (KDIGO) guideline definition[57, b]	EHR via chart review
Mortality	Secondary outcome	Hospital mortality	Administrative data
Length of stay	Secondary outcome	Duration of stay in the hospital	Administrative data
Readmissions	Secondary outcome	Within 30 post discharge	Administrative data
Other HAIs (central line-associated bloodstream infection)	Secondary outcome	During ICU or hospital stay	Routinely collected by infection control
Infection control interventions	Descriptive	Compliance with environmental cleaning, hand hygiene and contact precautions	Routinely collected by infection control with direct observations

Baseline proportion of CDI due to NAP-1 in ICUs and associated facilities	Secondary outcome	Obtained from hospital antibiograms or other infection prevention data	May be collected by infection control
Patient level variables			
Age	Descriptive	Years	Extracted from EHR
Sex	Descriptive	Male; Female; Unknown/Not provided	Extracted from EHR
Race	Descriptive	American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White[c]	Extracted from EHR
Ethnicity	Descriptive	Hispanic or Latino; Not Hispanic or Latino[c]	Extracted from EHR
Comorbidity and severity score	Descriptive	Charlson Comorbidity Index score[58, 59] and APACHE score[60, 61]	Extracted from EHR
Number of prior CDI	Descriptive	Number of prior cases of healthcare-associated CDI, confirmed by positive test	Extracted from EHR
Appropriateness of antibiotic use	Secondary outcome	Use is concordant with institutional guidelines as judged by 2 AS team members at each site.[62] A physician from the investigative team (NS) will adjudicate disagreements.[d]	Chart review of a sample of cases
Historical factors	Descriptive	Historical factors that may influence findings	Infection control and antibiotic stewardship data
Sars-CoV-2 (COVID-19) infection status	Descriptive	Positive/negative status	Extracted from EHR

[a] A single DOT will be recorded for each individual antibiotic administered to a patient on a given day. Antibiotic use will be normalized to patient days of therapy per 1000 patient-days (PD) as well as per patient admission.

[b] The KDIGO guideline defines AKI as any of the following: Increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or Increase in serum creatinine to ≤ 1.5 times baseline or urine volume < 0.5 mg/kg/hour for 6 hours[57]

[c] These categories are consistent with the US Office of Management and Budget minimum standards for maintaining, collecting, and presenting race and ethnicity for all grant projects defined in OMB Directive No. 15. The National Institutes of Health Grants Policy Statement supports the use of these categories.[63]

[d] The following published guidance will be used to judge appropriateness: the Hopkins "Four Moments in Antibiotic Decision-Making" approach: (1) Was antibiotic therapy indicated based on known clinical, microbiological, radiographic, and severity of illness findings of the patient? (2) Was the most appropriate empiric antibiotic regimen selected? (3) Was therapy appropriately adjusted or stopped after a reassessment by day 3 of antibiotics? (4) Was the duration of therapy appropriate for the infection being treated?[64] Given the intensive resources required for this endeavor, we will focus on sepsis treatment.

Aim 1: Statistical Analysis

Using 10.5 per 10,000 patient day CDI rate as the base value, reducing it by 50% based on the literature, and using a NR-SW cluster design, we will need monthly assessments, CDI months pre- and 12 months post-intervention, assuming 10 beds per ICU, in 6 ICUs to achieve power at around 0.80, with two-tailed alpha test at 0.05. We have selected a far more conservative sample size of 12 ICUs to detect an effect of less than 50% which may nevertheless be clinically meaningful, also allowing for ICU attrition. Simulation studies[65] have indicated that adequate power to detect effects in balanced data series, as few as 12 data points, may be reasonable for our regression discontinuity analysis in detecting program intervention level and trend change.

Multiple ICU units (12 ICUs) will be nested in 5 hospitals. This would typically provide a very small number of units to be modeled at a hospital-level, with not enough data to properly estimate the model. Therefore, we do not plan to establish a hospital level variable to attempt to account for this clustering. Hospitals, as well as ICU type will be included as a covariate.

We will use two analytic strategies, the first being a multilevel logit random effects model on the incidence of CDI of all ICUs sites, following procedures suggested by the Huynh, et al (2016) simulation for analysis of NR-SW designs.[50] All models will be constructed using MLwiN software Version 3.02.[66]

The second analytic approach will be to use interrupted time series analysis[67] for step-by-step CDI rates per ICU, using the 12 month pre- and 12 month post-intervention data. In this design, data are collected at multiple instances over time before and after an intervention is introduced to detect whether the intervention has an effect significantly greater than the underlying secular trend. Since we anticipate an abrupt and permanent change in the outcome after implementation of the intervention program, we propose regression discontinuity analysis using an autoregressive regression model. All interrupted time series models will be constructed using Stata's Version 14 routine interrupted time series analysis.[68]

Some sites will be subject to the effects of the COVID-19 pandemic of 2020-2021. Patient level data about COVID-19 status and percentage of ICU beds occupied by such patients will also be included in the data collection to facilitate analysis of changes to prescribing post-pandemic. Since COVID influence is time varying incorporation of the time varying agents into our time series model would be appropriate.

Aim 2: Data Collection

Data collection for the implementation evaluation and analysis will occur during Phases One and Two, simultaneous with intervention launch. Data sources will include (1) aggregated site contextual data (2) implementation process documentation, and (3) study feedback from site participants, using IRB-approved surveys, semi-structured interview and focus group prompts, and informed consent will be obtained from all participants. See Table 3 for a summary of data sources and study outcomes for the secondary aim.

Table 3. Implementation data sources and analysis

Domain	Instrument	Components	Outcome measures
Contextual site information	Site infection prevention practices	Infection prevention program, personnel and infrastructure; infection prevention and control activities; risk assessment; frequency of updates; educational outreach; active surveillance screening and procedure by organism; screening procedure for HAIs; pre-surgical decolonization procedures and surgical targets; contact precautions by organism; hand hygiene procedures, compliance and feedback; personal protective equipment (PPE) use; environmental cleaning procedures; surveillance reporting	Contextual information for: cross-site comparison; implementation analysis
	Site antibiotic stewardship practices	AS leadership support and infrastructure; AS educational updates; antibiotic indication documentation procedures; facility-specific treatment recommendations and monitoring; antibiotic time out precedures; pre-prescription program procedures; audit and feedback specifications and process; antibiotic utilization monitoring; antibiotic consumption monitoring and reports;	Contextual information for: cross-site comparison; implementation analysis

		antibiotic susceptibility testing; antibiogram data;	
	ICU information	ICU facility type and model; number of beds; ICU critical statistics (avg. length of stay, number of patients per year; patient days per year or month); ICU personnel information; ICU prescriber data; AS (pharmacist and infectious disease physician) support for ICU prescribers;	Contextual information for: cross-site comparison; implementation analysis
Implementation practices	Implementation diary	Timeline of pre- and post-implementation related activities, participants, and durations	Implementation analysis: timeline
	Site Startup Activities	Identification of site contacts and implementation roles; pre-intervention support and task status	Implementation analysis: timeline
	Check-in meeting notes	Record of changes to sites AS or IP practices; barriers and facilitators to introducing intervention	Implementation analysis: barriers and facilitators
	Usability test	Pre-launch feedback on BPA from primary ICU prescribers, performed in the playground environment of the EHR	Implementation analysis: integration into work systems; support
Intervention assessment	Surveys	Acceptance of BPA; complexity; ease of use; need for technical support; integration into EHR; consistency; confidence about use;	Implementation analysis
	Semi-structured interviews with BPA users and AS support personnel	Pluses and minuses of intervention implementation (notification, training/education, release), role in implementation; effect of BPA integration into work system and workflow (positives/negatives); effect of BPA on workload, teamwork, changes	Implementation analysis
	Focus groups	ICU healthcare providers grouped by specialty discuss their experiences of the FQ PPA intervention focusing on pluses and minuses of the implementation process	Implementation analysis

Aim 2: Implementation Analysis

The secondary outcome measures of this intervention include evaluating the effectiveness of the implementation processes at each site using the SEIPS conceptual framework. A multiple case study design[44, 45, 69] with a mixed methods approach[41, 46, 47] will be used to evaluate the implementation process, with each participating ICU constituting a single site. The SEIPS framework will be used to relate these characteristics to the effectiveness outcomes at each site in a cross-case analysis (Figure 2).

Figure 2. Systems Engineering Initiative for Patient Safety (SEIPS) Framework - Fluoroquinolone PPA Implementation in Acute Care Settings.

The concurrent implementation of the FQ intervention and evaluation of its impact and corresponds to the convergent parallel trial design in mixed methods research[46, 47, 70] in which quantitative and qualitative data are collected simultaneously. The final outcome of this analysis will be a "thick" description of implementation with varying levels of success as measured by the primary outcomes. "Thick" description refers to the use of qualitative methods that provide depth of understanding of both process and the inner and outer contexts of intervention implementation, to complement the breadth of understanding allowed by quantitative analysis of clinical data.[70] Site-specific data will be combined in a cross-case analysis table in an Excel spreadsheet, in an adaptation of the predictor-outcome-consequences matrix of Miles and Huberman.[48] We will use a systematic comparative pattern analysis method to iteratively compare and emphasize the combination of potential contributing factors that

function together as a system.[69] This is an important feature of the analysis that fits with the systems approach, which is at the core of the SEIPS model.[41] Analysis of the compiled data will be performed by a team of researchers with varied expertise in implementation science, human factors and systems engineering, and infectious disease. The triangulation with multiple analysts will enhance the quality of the analysis and ensure its rigor.[70, 71]

Discussion

We expect this study to demonstrate that the FQ PPA intervention has resulted in decreases in FQ usage in ICU settings, and lowered ICU-onset and HO-onset CDI rates. We also expect to have collected rich data on implementation to guide future FQ PPA interventions, including important information on barriers and strategies to overcome them.

At the project conclusion, we will have (1) assessed the effects on CDI rates of the FQ PPA implementation-intervention trial and (2) evaluated the most effective implementation processes for introducing this FQ PPA in ICU settings. The knowledge from this project could benefit subsequent projects focused on instituting FQ PPA in acute care settings, and improve the quality of AS programs nationally. The integration of the FQ PPA into CDS technologies with real-time clinical expertise availability has the potential to improve the quality of antibiotic prescribing throughout entire hospital systems as well. Given the complexity of this intervention, the findings may not be applicable to the implementation of simpler FQ PPA efforts. However, there are critical gaps in the knowledge of how to best target CDI with AS interventions, which this study will address.

The evolving COVID-19 pandemic of 2020 is likely to affect site recruitment and results for this trial. Amongst other effects, prescribing practices for patients with suspected or confirmed COVID-19 infection in the ICU may influence antibiotic use. We will attempt to address this by comparing site prescribing practices pre -COVID-19 and post-COVID-19.

Ethics and dissemination

Ethical approval for this study was obtained from the University of Wisconsin-Madison Health Sciences Institutional Review Board (Protocol Version: 2018-0852-CP015). Individual sites may choose to undergo their own internal review process or cede to the IRB of the University of Wisconsin. The study protocol was approved on July 24, 2018 and this manuscript reports on the most updated version of the protocol approved on October 19, 2020. All participant sites will be informed prior to enrollment that participation is completely voluntary, that they can withdraw from participation at any time, and that their decision to participate or not will not affect their health care in any way.

Upon completion of the study, we will present the results at major scientific conferences and will publish the results in peer-reviewed journals.

Author contributions

NS, PC, RB, AL, JO, and LS conceived of the study concept and design. VP drafted the overall protocol, with critical input from NS and RB for study design, recruitment, and statistical analysis. RB drafted protocol sections for statistical analyses; and PC for implementation

analysis. All authors provided critical feedback and approved the final version of the manuscript.

Competing Interests

None declared.

Funding statement

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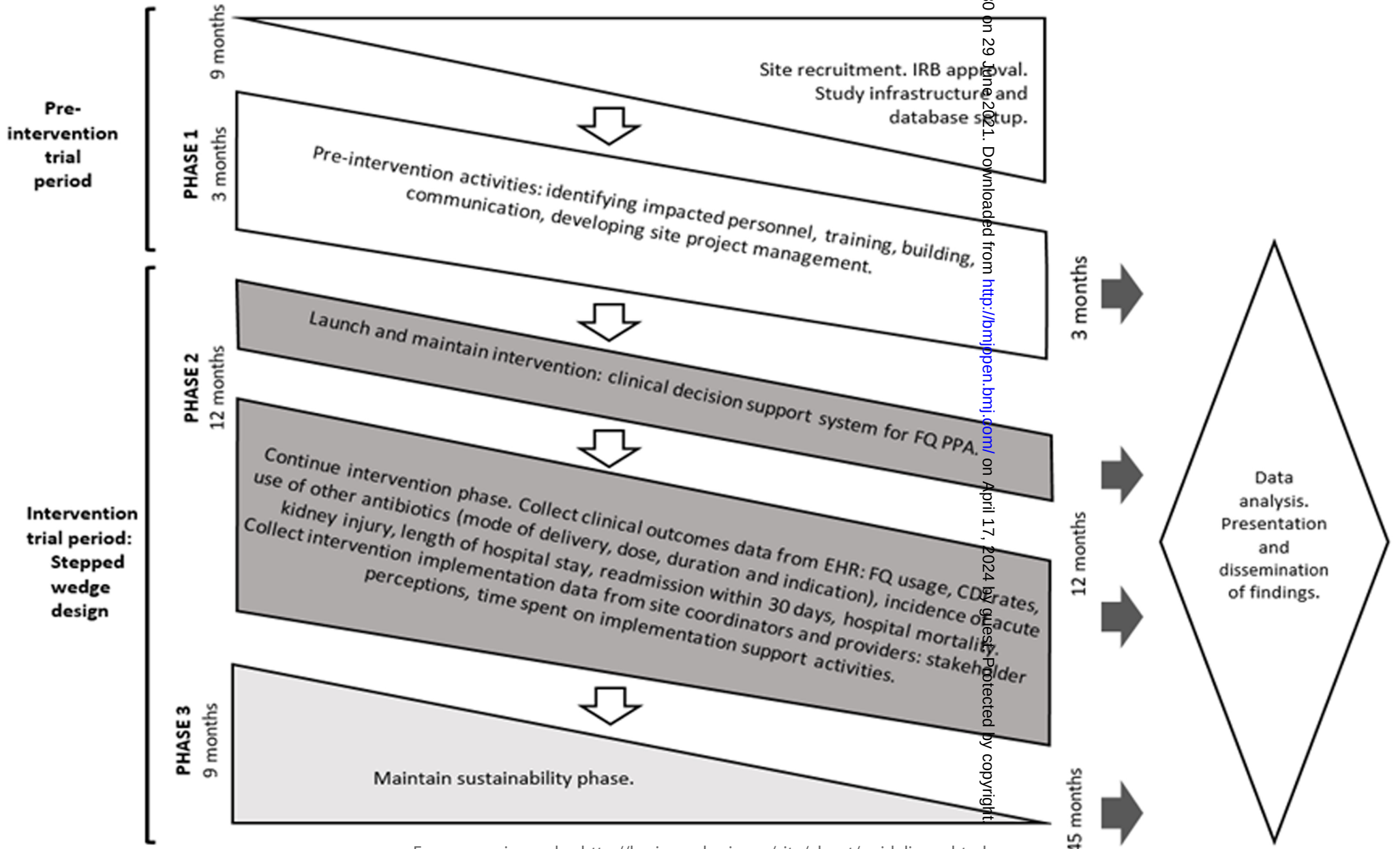

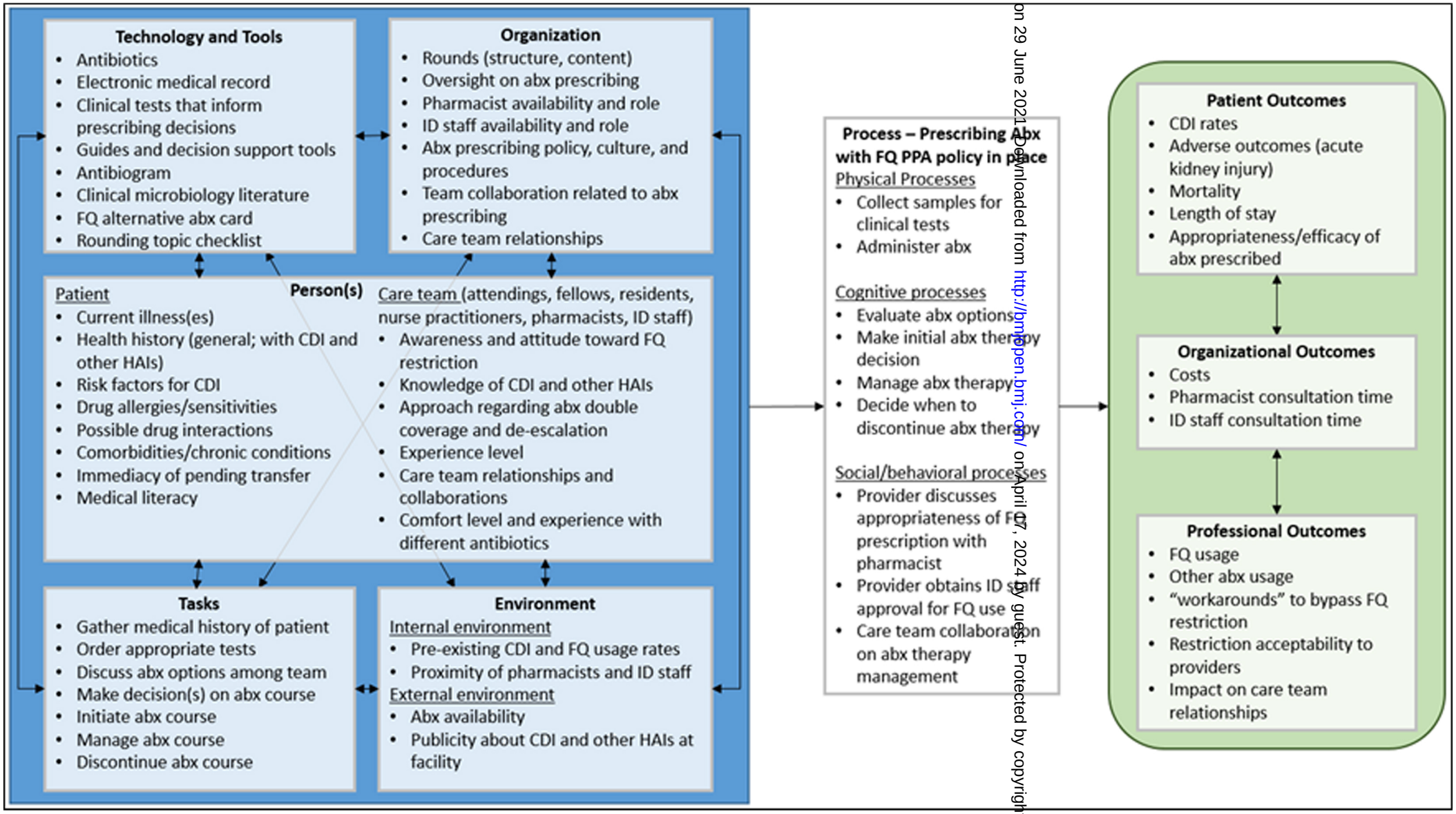

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	NCT03848689 at clinicaltrials.gov
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	23
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	10

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg,	6-7

		systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	19
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection,			

management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-24
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	26
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	26
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	26
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	26

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Notes:

- 2a: NCT03848689 at clinicaltrials.gov This checklist was completed on 30. October 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

A study protocol for decreasing ICU-associated Clostridioides difficile infection through fluoroquinolone restriction: The FIRST trial

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Manuscript ID	bmjopen-2020-046480.R2
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A study protocol for decreasing ICU-associated *Clostridioides difficile* infection through fluoroquinolone restriction: The FIRST trial

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Abstract

Introduction: Clostridioides difficile infection (CDI) is the one of the most common healthcare-associated infection (HAI) in the USA, having high incidence in intensive care units (ICU). Antibiotic use increases CDI risk, with fluoroquinolones (FQ) particularly implicated. In healthcare settings, antibiotic stewardship (AS) and infection control interventions are effective for CDI control, but there is little evidence regarding the most effective AS interventions. Pre-prescription authorization (PPA) restricting FQs is a potentially promising AS intervention to reduce CDI. This study will evaluate the effectiveness of a FQ PPA intervention in reducing CDI rates in adult ICUs compared with pre-intervention care, and evaluate implementation effectiveness using a human-factors and systems engineering model.

Methods and analysis: This is a multisite stepped-wedge cluster effectiveness-implementation clinical trial. The trial will take place in 12 adult medical-surgical ICUs with ≥10 beds, Epic as electronic health record (EHR), and preexisting AS programs. Sites will receive facilitated implementation support over the 15-month trial period, succeeded by 9 months follow-up. The intervention comprises a clinical decision support system for FQ PPA, integrated into site EHRs. Each ICU will be considered a single site, and all ICU admissions included in analysis. Clinical data will be extracted from EHRs throughout the trial and compared to the corresponding pre-trial period, which will constitute the baseline for statistical analysis. Outcomes will include ICU-onset CDI rates, FQ days of therapy (DOT), alternative antibiotic DOT, average length of stay,

and hospital mortality. The study team will also collect implementation data to assess implementation effectiveness using the Systems Engineering Initiative for Patient Safety model.

Ethics and dissemination: The trial was approved by the Institutional Review Board at the University of Wisconsin-Madison (2018-0852-CP015). Results will be made available to participating sites, funders, infectious disease societies, critical care societies, and other researchers.

Trial registration: NCT03848689; Pre-results.

Article Summary

Strengths and limitations of this study

- FIRST will provide one of the few national, multi-site, comprehensive studies that investigate the effect on intensive care unit-associated-CDI of fluoroquinolone pre-prescription authorization integrated as a computerized decision support tool.
- Our trial design will allow us to look at changes in outcome measures over time at the same site, delineating a temporal sequence to ICU-associated and hospital associated CDI, providing more evidence for causality.

- Our approach simultaneously introduces antibiotic stewardship FQ prescribing best-practices, and assesses the introduction of these practices, facilitating continuous implementation improvement.
- The primary limitation to this trial is a slow-down in recruitment rates with the SARS-coV-2 Covid-19 pandemic, and the uncertain effects of this pandemic upon current ICU sites.

Keywords: Hospital associated *Clostridiodes difficile* infection, antibiotic stewardship, fluoroquinolone restriction, pre-prescription authorization, implementation effectiveness

Introduction

Background and rationale

Clostridioides difficile infection (CDI) is the most prevalent healthcare-associated infection in the United States[1] and CDI rates are consistently higher in intensive care unit (ICU) settings.[2] CDI represents a serious threat to patient safety,[3] and excess costs to acute care hospitals in the US are estimated to be $4.8 billion annually.[4] Antibiotics are among the most commonly prescribed medications in ICUs, and antibiotic exposure is the primary risk factor for CDI.[5-7] This is due to the intestinal dysbiosis caused by antibiotics, particularly broad-spectrum agents,[7, 8] rendering individuals more vulnerable to CDI.[7]

Antibiotic stewardship (AS) interventions are essential to reducing the burden of CDI.[9-12] The goals of AS are to enhance patient outcomes and reduce the inappropriate and over-prescribing of antibiotics.[13] An analysis of national data indicated that reducing prescription of

broad-spectrum antibiotics by an estimated 30% would prevent 26% of CDI related to inpatient antibiotic use.[11] This would require only a 5% reduction of overall antibiotic use.[11]

While there is considerable literature to support the use of infection prevention interventions for reducing CDI,[14] there remain gaps about the impact and implementation of AS interventions specific to CDI. Existing research has yielded unclear and sometimes conflicting results regarding impact of AS interventions on CDI rates.[14-22] Moreover, data on patient outcomes in response to AS interventions are inconsistently defined and limited.[15, 21] For these reasons, further evaluation is needed to better understand which specific AS interventions will have the greatest impact on CDI rates.[14, 15] Potential AS strategies promising for CDI reduction include pre-prescription authorization (PPA) and post-prescription review and feedback (PPRF).[15, 16, 22-34]

Of the antibiotic classes, FQs are one of the most frequently utilized in inpatient acute care facilities, where they are prescribed to 16.2% of patients.[35] FQ usage markedly increases the risk of CDI,[27-30, 36] and reductions in FQ use are associated with decreased HO-CDI rates in US acute care hospitals.[37] Rising CDI rates in US hospitals can in part be attributed to the FQ-resistant strain 027/BI/NAP1,[3] which accounts for the largest proportion of healthcare facility-onset CDI (HO-CDI) cases nationally (30.7%).[3]

Study outcomes and measures

The trial described in this protocol is designed to implement a FQ PPA intervention, and evaluate its implementation effectiveness and impact on CDI rates in adult medical-surgical ICU

settings. This approach was chosen because restrictive AS interventions like PPA are likely to be effective, but implementation is often complex and variable between studies, making implementation evaluation difficult. We propose the integration of a FQ PPA into the electronic health record (EHR) using clinical decision support (CDS) technologies. CDS technologies have demonstrated improvements in patient outcomes in a variety of healthcare settings.[38-40] We hypothesize that this FQ PPA intervention will result in decreased CDI rates during the intervention period, and that quality improvement efforts will be enhanced by UW study-team external implementation facilitation at each site.

The primary objective is to evaluate the effectiveness of this FQ PPA intervention in reducing ICU-onset and healthcare facility-onset CDI (HO-CDI) rates in adult ICUs compared with usual care. The secondary objective is to evaluate the effectiveness of the implementation of this intervention using the Systems Engineering Initiative for Patient Safety (SEIPS) model.[41]

Methods

Study Aims and Hypothesis

The overall hypothesis of this study is that a FQ PPA intervention is an effective strategy to reduce CDI rates in the ICU setting. The primary aim of the trial is to determine the impact of FQ PPA on ICU-onset and HO-CDI rates and other clinical outcomes compared with usual care in medical-surgical adult ICUs enrolled in this trial. Consistent with Structured Taskforce of Experts Working at Reliable Standards for Stewardship (STEWARDS) Panel recommendations, we will collect ICU-onset CDI as a subset of HO-CDI rates, HO-CDI, and healthcare-associated CDI (HA-CDI) as measures of trial effects.[42] We will also collect antibiotic utilization data measured in

days of therapy (DOT) per patient admission, and per patient-days, for both FQs and their most common alternatives as primary targets of the intervention.

The secondary aim of the trial is to facilitate and evaluate the implementation process, uptake, and effectiveness of the FQ PPA as a complex behavioral intervention using the SEIPS model.[41] SEIPS provides a broad and flexible way to characterize and evaluate work systems and care processes and the complex relationships among them using five work system elements: people, tools and technologies, tasks, organizational factors, and environmental factors.[43] This model will be used to characterize and evaluate the AS intervention and its impact on care processes and various patient, organizational, and professional outcomes to produce a "thick" description of implementation processes[44-47] at each of the sites (described later in this article). These characteristics will then be related to clinical outcomes of the primary aim in a cross-case analysis.[45, 48]

We used the SPIRIT reporting guidelines in the preparation of this manuscript.[49]

Overall Study Design

A non-randomized stepped wedge (NR-SW) cluster design will be used, embedded within an effectiveness-implementation hybrid type 2 trial of ICUs that have elected to implement the FQ PPA.[50] This design is appropriate as it allows us to simultaneously evaluate the FQ PPA's clinical effects and the impact of the implementation approach on intervention adoption. As all ICUs were planning to implement FQ AS interventions for quality improvement practices, the NR-SW wedge design allows each site to receive the trial intervention while serving as its own control, thereby maintaining strong internal validity.

The trial will involve three phases at each ICU site. Phase One is a 3-month pre-FQ PPA preparatory period for external facilitation of the implementation, prescriber education, building the FQ PPA clinical decision support BPA, and early contextual and implementation data collection. Phase Two is the 12-month intervention period during which the FQ PPA-BPA goes live, over which time both routinely collected clinical EHR data and implementation data will be regularly collected. Phase Three is a sustainability phase during which sites develop and maintain sustainability action plans, and can choose to continue the PPA policy with no further implementation support from the trial team. This sequence will be repeated for each of the sites until all have completed the intervention phase of the trial. Clinical variables and outcomes for the corresponding 12-month pre-intervention period will constitute the baseline for comparison with the Phase Two intervention period. The influences upon implementation and its effectiveness at each site will be assessed using a mixed-methods approach. Figure 1 provides a schematic overview of the study design and method.

Figure 1. Schematic depiction of the trial design and procedures.

Trial Organization

The Steering Committee (SC): The SC will be chaired by PI Professor Nasia Safdar, and include lead biostatistician, Professor Roger Brown, co-investigators (Dr. Pascale Carayon, Dr. Lucas Schulz, Dr. Aurora Pop-Vicas) and other study personnel (Dr. Vishala Parmasad, Dr. Alex Lepak, Michele Zimbric and Kendra Haight). The SC will meet face-to-face once before study initiation and monthly via teleconference throughout the study. The SC will be responsible for reviewing

study progress and if necessary, agreeing to protocol changes to facilitate smooth running of the study.

The Data Coordinating Center (DCC): The DCC will provide expertise and support for the trial in data management, data verification, quality control and assurance, information technology for communication and trial monitoring, and statistical methods for design including statistical analyses, preparation of results in tabular and graphical formats for presentation, and publication of findings from the trial. The DCC will be located in the University of Wisconsin-Madison, led by study biostatistician Professor Roger Brown and data manager Fauzia Osman. The UW-Madison team will be responsible for oversight of the DCC activities.

The Clinical Coordinating Center (CCC): The CCC will be responsible for overall study execution: protocol refinement, comprehensive site implementation facilitation, medical monitoring, handling of potential patient-related issues, interfacing with the DCC, and coordination with AHRQ. The CCC will be physically located at UW-Madison and led by the PI and study lead, Dr. Vishala Parmasad.

Data Collection and Management: The electronic case report forms (eCRFs) will be finalized by the DCC before being reviewed and approved by the study team. Data collected at the clinical sites will be de-identified recorded on eCRFs and entered using the clinical trial data management system. Study investigators will have access to the final trial dataset, and site personnel will have access to site-specific data.

Site Monitoring: We are planning site virtual initiation visits prior to site enrollment. In addition, we are planning to audit 10% of cases, and conduct site audits for cause or on a risk-based priority. All regulatory aspects will be monitored.

Adverse Event Monitoring: Adverse event (AE) reporting, such as side effects from alternative antibiotics or inappropriate antibiotic use, will follow established site-specific guidelines for retrospective AE monitoring and reporting. Existing research on antibiotic stewardship interventions, including FQ PPA, indicates that these types of interventions do not have adverse impacts on patient outcomes. While the antibiotics patients receive will be impacted by the FQ PPA intervention, the alternative antibiotics available to providers all fall within best practice guidelines and the possible risks associated with these antibiotics are in equipoise with those associated with FQ. As the purpose of this study is to optimize adherence to established AS best practices, real-time adverse events monitoring was not considered necessary. Once the study is in place, an independent, ad-hoc Drug Safety and Monitoring Board (DSMB) will review a sample of charts from each study site. These charts will be extracted from the study site by site personnel and de-identified before being provided to the UW study team for review.

Patient and Public Involvement

The UW Team has consistently worked with a patient stakeholder group, The Patients Engaged in Education and Research (PEER) Group, soliciting feedback regarding patient priorities in healthcare associated infection prevention. The overall goals of this study are in line with

expressed patient priorities of improving antibiotic stewardship and decreasing CDI, however this study specifically targets the prescribing practice of ICU providers. Patients were thus not involved in the design, recruitment, conduct, or assessment of the study. The results of this study will be disseminated back to patient stakeholders through venues such as meetings, patient-provider conferences, and working with the Madison Patient Education Resource Center.

Study Population, inclusion and exclusion criteria

Adult general medical and surgical ICU sites are the targets of this trial. Participant sites must have a pre-existing AS program with pharmacist and infectious disease (ID) physician support and their EHR vendor as Epic Systems Corporation. Their EHR must have the ability to extract antibiotic usage data (days of therapy), required outcome data (CDI, mortality, length of ICU stay), and data on indications for antibiotic use. They must additionally be adherent to best practices for infection control relevant to CDI. Sites are considered ineligible to participate if they are already restricting FQ or another antibiotic associated with CDI risk. These criteria were selected so that the intervention could be implemented in a standardized manner. The use of Epic Systems Corporation as an EHR vendor was necessary to ensure the changes necessary to the EHR will be feasible at each site. The UW study team will provide templates for

and information technology consultations on the required EHR changes and data extraction processes.

Once initiated, the intervention will be applied to all patients admitted to the ICU and all healthcare workers involved in antibiotic prescribing in that ICU. The intervention and usual care strategies will be allocated at the ICU level, thus inclusion and exclusion criteria apply to ICUs, not to individual patients. Assigning ICUs rather than individuals to the intervention is appropriate given horizontal transmission of *C. difficile.*

Recruitment and Consent

We chose a total of 12 ICUS to participate in the trial to ensure a patient sample size large enough to detect clinically meaningful and statistically significant differences in CDI outcomes between the intervention and usual care, and to account for site attrition. Recruitment emails will be sent out via regional and national research networks, pharmacist networks, and AS networks. Informed consent will be obtained by study lead from all personnel participating in interviews and surveys about implementation, and collected data will be de-identified before inclusion in the study. Recruitment will take place on a rolling basis to account for variations in time to completion of pre-trial regulatory activities.

Study Intervention

This multicomponent study constitutes a suite of resources for the introduction and assessment of FQ prescribing best practices in adult ICUs, via a FQ PPA structured around a

CDS system within site EHRs. The trial team supports the implementation process at each site and facilitates the development of site-specific CDS FQ PPA protocols.

The FQ PPA CDS intervention constitutes a best practices alert (BPA) that appears when providers attempt to prescribe FQs in the ICU. The BPA informs providers that FQ use is restricted, and provides links to select alternative antibiotics. Providers can alternatively contact a designated member of the hospital AS team to discuss the choice of drug via the BPA. The BPA and order set will be constructed to allow tracking of non-adherence to the FQ PPA policy, allowing the measurement of fidelity to the intervention. FQs will be discontinued on patients who are already on a FQ when they are transferred to the ICU.

Before and during the implementation of the FQ PPA policy at each site, the trial team will engage in the external implementation facilitation of this intervention, through supportive activities consistent with evidence-based implementation principles (Table 1).[51, 52] This approach was purposefully developed by examining relevant implementation literature.[52-55]

Table 1. Evidence-based Implementation Principles

Implementation principles	What will be done at each site
Top management commitment	Immediately prior to initiating the PPA, we will ask each site's leadership to communicate support for the intervention. Depending on the site, this could include the board of directors, medical staff boards of governance, ICU leadership, the ICUs' quality improvement committee, and/or the pharmacy and therapeutics team.
User participation	After we identify site coordinators, we will ask them to identify the attendings, fellows, residents, advanced practice providers, pharmacists, and ID staff from the AS team who will be impacted by the PPA.

Communication and feedback	We will set up conference calls with these providers to identify champions, and ask them to describe any barriers to and facilitators of implementing the PPA. Individuals identified as possible champions and opinion leaders will be contacted. We will engage them to identify ways they might promote the intervention throughout the trial.
Training	We will set up conference calls via webinar with relevant providers in order to provide training. We will have separate coaching sessions with the unit pharmacists and the AS team to handle calls/questions from providers regarding FQ prescribing. We will also distribute a toolkit to providers that will include a summary of research supporting FQ PPA, data on their ICU's CDI and FQ usage rates, a FQ alternative antibiotics card, a cross-table antibiogram and links to relevant prescribing guides and decision support tools.
Learning	Once these activities have been completed, we will closely analyze the barriers and facilitators at each site and work with site coordinators to address the barriers and leverage facilitators to the greatest extent possible. Once the PPA policy has been initiated at each site we will continue to provide support to aid the implementation of the PPA policy. We will also hold monthly phone calls with the site coordinators to discuss how any emerging barriers can be addressed while maintaining fidelity.
Project management	We will identify coordinators at each site who will act as the primary contact for the trial. We will work with the coordinators to identify barriers and facilitators for the implementation of the PPA policy at their sites. We will also ask the coordinators to identify staff who seem enthusiastic about the intervention that may act as champions at their site.

Usual care

Usual care for this trial will include no active restriction of FQ use. Sites may still choose to use post prescription feedback for FQ if that is their usual practice. There may be restriction of other antibiotics as per a site's usual practice and an active AS program must be in place. Given expected variation in usual practice, we will collect data on usual AS and infection prevention practices at each site to understand the spectrum of usual care.

Data Collection and Analysis

Aim 1: Data Collection

For the primary aim, data will be extracted from each site's Clarity database derived from the PennChart (Epic) EHR application. The trial team will provide each site with a standardized data extraction manual and Microsoft SQL coding-logic document delineating the required data variables. Routinely collected patient-level clinically generated data will be extracted for the 12-month Phase Two intervention period, and the corresponding 12-month pre-intervention period.

We will collect incidence of HO-CDI, location-specific ICU-onset CDI, and HA-CDI. In order to more closely associate the effects on CDI rates with a site's antibiotic use, the fidelity of the intervention will be confirmed by measuring FQ and other antibiotic usage in DOT per patient admission and DOT per 1000 patient-days. To evaluate both the positive and negative clinical outcomes of this intervention to participating ICUs, mortality, readmissions, hospital length of stay, and the incidence of other (non-CDI) HAIs will also be assessed. Table 2 shows the data variables that will be collected. The de-identified clinical data will be sent to the trial team via a personal health information secure website for statistical analysis.

Table 2. Variables to be collected for Aim 1 analysis

Unit (or hospital)-level variables	Type of variable	Operational Definition	How extracted

Healthcare facility-onset CDI (HO-CDI) with ICU-onset	Primary outcome	Positive test for CDI from ICU specimen sent from symptomatic patient, on or after day 4 of admission to healthcare facility [56]	Routinely collected by infection control
Healthcare facility-onset CDI (HO-CDI)	Primary outcome	Positive test for CDI from symptomatic patient on or after day 4 of admission to healthcare facility.[56]	Routinely collected by infection control
Healthcare-associated CDI (HA-CDI)	Primary outcome	Positive test for CDI from a symptomatic patient who was discharged from the facility ≤ 4 weeks prior to date of stool specimen collection[56]	Routinely collected by infection control
FQ usage	Secondary outcome	Days of therapy (DOT) per patient admission and DOT per 1000 Patient-Days (PD)[a]	EHR-routinely collected by antibiotic stewardship
All other antibiotic usage	Secondary outcome	DOT per patient admission and DOT per 1000 PD[a]	EHR-routinely collected by antibiotic stewardship
AKI	Secondary outcome	Kidney Disease Improving Global Outcomes (KDIGO) guideline definition[57, b]	EHR via chart review
Mortality	Secondary outcome	Hospital mortality	Administrative data
Length of stay	Secondary outcome	Duration of stay in the hospital	Administrative data
Readmissions	Secondary outcome	Within 30 post discharge	Administrative data
Other HAIs (central line-associated bloodstream infection)	Secondary outcome	During ICU or hospital stay	Routinely collected by infection control
Infection control interventions	Descriptive	Compliance with environmental cleaning, hand hygiene and contact precautions	Routinely collected by infection control with direct observations

Baseline proportion of CDI due to NAP-1 in ICUs and associated facilities	Secondary outcome	Obtained from hospital antibiograms or other infection prevention data	May be collected by infection control
Patient level variables			
Age	Descriptive	Years	Extracted from EHR
Sex	Descriptive	Male; Female; Unknown/Not provided	Extracted from EHR
Race	Descriptive	American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White[c]	Extracted from EHR
Ethnicity	Descriptive	Hispanic or Latino; Not Hispanic or Latino[c]	Extracted from EHR
Comorbidity and severity score	Descriptive	Charlson Comorbidity Index score[58, 59] and APACHE score[60, 61]	Extracted from EHR
Number of prior CDI	Descriptive	Number of prior cases of healthcare-associated CDI, confirmed by positive test	Extracted from EHR
Appropriateness of antibiotic use	Secondary outcome	Use is concordant with institutional guidelines as judged by 2 AS team members at each site.[62] A physician from the investigative team (NS) will adjudicate disagreements.[d]	Chart review of a sample of cases
Historical factors	Descriptive	Historical factors that may influence findings	Infection control and antibiotic stewardship data
Sars-CoV-2 (COVID-19) infection status	Descriptive	Positive/negative status	Extracted from EHR

[a] A single DOT will be recorded for each individual antibiotic administered to a patient on a given day. Antibiotic use will be normalized to patient days of therapy per 1000 patient-days (PD) as well as per patient admission.

[b] The KDIGO guideline defines AKI as any of the following: Increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or Increase in serum creatinine to ≤ 1.5 times baseline or urine volume < 0.5 mg/kg/hour for 6 hours[57]

[c] These categories are consistent with the US Office of Management and Budget minimum standards for maintaining, collecting, and presenting race and ethnicity for all grant projects defined in OMB Directive No. 15. The National Institutes of Health Grants Policy Statement supports the use of these categories.[63]

[d] The following published guidance will be used to judge appropriateness: the Hopkins "Four Moments in Antibiotic Decision-Making" approach: (1) Was antibiotic therapy indicated based on known clinical, microbiological, radiographic, and severity of illness findings of the patient? (2) Was the most appropriate empiric antibiotic regimen selected? (3) Was therapy appropriately adjusted or stopped after a reassessment by day 3 of antibiotics? (4) Was the duration of therapy appropriate for the infection being treated?[64] Given the intensive resources required for this endeavor, we will focus on sepsis treatment.

Aim 1: Statistical Analysis

Using 10.5 per 10,000 patient day CDI rate as the base value, reducing it by 50% based on the literature, and using a NR-SW cluster design, we will need monthly assessments, CDI months pre- and 12 months post-intervention, assuming 10 beds per ICU, in 6 ICUs to achieve power at around 0.80, with two-tailed alpha test at 0.05. We have selected a far more conservative sample size of 12 ICUs to detect an effect of less than 50% which may nevertheless be clinically meaningful, also allowing for ICU attrition. Simulation studies[65] have indicated that adequate power to detect effects in balanced data series, as few as 12 data points, may be reasonable for our regression discontinuity analysis in detecting program intervention level and trend change.

Multiple ICU units (12 ICUs) will be nested in 5 hospitals. This would typically provide a very small number of units to be modeled at a hospital-level, with not enough data to properly estimate the model. Therefore, we do not plan to establish a hospital level variable to attempt to account for this clustering. Hospitals, as well as ICU type will be included as a covariate.

We will use two analytic strategies, the first being a multilevel logit random effects model on the incidence of CDI of all ICUs sites, following procedures suggested by the Huynh, et al (2016) simulation for analysis of NR-SW designs.[50] All models will be constructed using MLwiN software Version 3.02.[66]

The second analytic approach will be to use interrupted time series analysis[67] for step-by-step CDI rates per ICU, using the 12 month pre- and 12 month post-intervention data. In this design, data are collected at multiple instances over time before and after an intervention is introduced to detect whether the intervention has an effect significantly greater than the underlying secular trend. Since we anticipate an abrupt and permanent change in the outcome after implementation of the intervention program, we propose regression discontinuity analysis using an autoregressive regression model. All interrupted time series models will be constructed using Stata's Version 14 routine interrupted time series analysis.[68]

Some sites will be subject to the effects of the COVID-19 pandemic of 2020-2021. Patient level data about COVID-19 status and percentage of ICU beds occupied by such patients will also be included in the data collection to facilitate analysis of changes to prescribing post-pandemic. Since COVID influence is time varying incorporation of the time varying agents into our time series model would be appropriate.

Aim 2: Data Collection

Data collection for the implementation evaluation and analysis will occur during Phases One and Two, simultaneous with intervention launch. Data sources will include (1) aggregated site contextual data (2) implementation process documentation, and (3) study feedback from site participants, using IRB-approved surveys, semi-structured interview and focus group prompts, and informed consent will be obtained from all participants. See Table 3 for a summary of data sources and study outcomes for the secondary aim.

Table 3. Implementation data sources and analysis

Domain	Instrument	Components	Outcome measures
Contextual site information	Site infection prevention practices	Infection prevention program, personnel and infrastructure; infection prevention and control activities; risk assessment; frequency of updates; educational outreach; active surveillance screening and procedure by organism; screening procedure for HAIs; pre-surgical decolonization procedures and surgical targets; contact precautions by organism; hand hygiene procedures, compliance and feedback; personal protective equipment (PPE) use; environmental cleaning procedures; surveillance reporting	Contextual information for: cross-site comparison; implementation analysis
	Site antibiotic stewardship practices	AS leadership support and infrastructure; AS educational updates; antibiotic indication documentation procedures; facility-specific treatment recommendations and monitoring; antibiotic time out precedures; pre-prescription program procedures; audit and feedback specifications and process; antibiotic utilization monitoring; antibiotic consumption monitoring and reports;	Contextual information for: cross-site comparison; implementation analysis

		antibiotic susceptibility testing; antibiogram data;	
	ICU information	ICU facility type and model; number of beds; ICU critical statistics (avg. length of stay, number of patients per year; patient days per year or month); ICU personnel information; ICU prescriber data; AS (pharmacist and infectious disease physician) support for ICU prescribers;	Contextual information for: cross-site comparison; implementation analysis
Implementation practices	Implementation diary	Timeline of pre- and post-implementation related activities, participants, and durations	Implementation analysis: timeline
	Site Startup Activities	Identification of site contacts and implementation roles; pre-intervention support and task status	Implementation analysis: timeline
	Check-in meeting notes	Record of changes to sites AS or IP practices; barriers and facilitators to introducing intervention	Implementation analysis: barriers and facilitators
	Usability test	Pre-launch feedback on BPA from primary ICU prescribers, performed in the playground environment of the EHR	Implementation analysis: integration into work systems; support
Intervention assessment	Surveys	Acceptance of BPA; complexity; ease of use; need for technical support; integration into EHR; consistency; confidence about use;	Implementation analysis
	Semi-structured interviews with BPA users and AS support personnel	Pluses and minuses of intervention implementation (notification, training/education, release), role in implementation; effect of BPA integration into work system and workflow (positives/negatives); effect of BPA on workload, teamwork, changes	Implementation analysis
	Focus groups	ICU healthcare providers grouped by specialty discuss their experiences of the FQ PPA intervention focusing on pluses and minuses of the implementation process	Implementation analysis

Aim 2: Implementation Analysis

The secondary outcome measures of this intervention include evaluating the effectiveness of the implementation processes at each site using the SEIPS conceptual framework. A multiple case study design[44, 45, 69] with a mixed methods approach[41, 46, 47] will be used to evaluate the implementation process, with each participating ICU constituting a single site. The SEIPS framework will be used to relate these characteristics to the effectiveness outcomes at each site in a cross-case analysis (Figure 2).

Figure 2. Systems Engineering Initiative for Patient Safety (SEIPS) Framework - Fluoroquinolone PPA Implementation in Acute Care Settings.

The concurrent implementation of the FQ intervention and evaluation of its impact and corresponds to the convergent parallel trial design in mixed methods research[46, 47, 70] in which quantitative and qualitative data are collected simultaneously. The final outcome of this analysis will be a "thick" description of implementation with varying levels of success as measured by the primary outcomes. "Thick" description refers to the use of qualitative methods that provide depth of understanding of both process and the inner and outer contexts of intervention implementation, to complement the breadth of understanding allowed by quantitative analysis of clinical data.[70] Site-specific data will be combined in a cross-case analysis table in an Excel spreadsheet, in an adaptation of the predictor-outcome-consequences matrix of Miles and Huberman.[48] We will use a systematic comparative pattern analysis method to iteratively compare and emphasize the combination of potential contributing factors that

function together as a system.[69] This is an important feature of the analysis that fits with the systems approach, which is at the core of the SEIPS model.[41] Analysis of the compiled data will be performed by a team of researchers with varied expertise in implementation science, human factors and systems engineering, and infectious disease. The triangulation with multiple analysts will enhance the quality of the analysis and ensure its rigor.[70, 71]

Discussion

We expect this study to demonstrate that the FQ PPA intervention has resulted in decreases in FQ usage in ICU settings, and lowered ICU-onset and HO-onset CDI rates. We also expect to have collected rich data on implementation to guide future FQ PPA interventions, including important information on barriers and strategies to overcome them.

At the project conclusion, we will have (1) assessed the effects on CDI rates of the FQ PPA implementation-intervention trial and (2) evaluated the most effective implementation processes for introducing this FQ PPA in ICU settings. The knowledge from this project could benefit subsequent projects focused on instituting FQ PPA in acute care settings, and improve the quality of AS programs nationally. The integration of the FQ PPA into CDS technologies with real-time clinical expertise availability has the potential to improve the quality of antibiotic prescribing throughout entire hospital systems as well. Given the complexity of this intervention, the findings may not be applicable to the implementation of simpler FQ PPA efforts. However, there are critical gaps in the knowledge of how to best target CDI with AS interventions, which this study will address.

The evolving COVID-19 pandemic of 2020 is likely to affect site recruitment and results for this trial. Amongst other effects, prescribing practices for patients with suspected or confirmed COVID-19 infection in the ICU may influence antibiotic use. We will attempt to address this by comparing site prescribing practices pre -COVID-19 and post-COVID-19.

Ethics and dissemination

Ethical approval for this study was obtained from the University of Wisconsin-Madison Health Sciences Institutional Review Board (Protocol Version: 2018-0852-CP015). Individual sites may choose to undergo their own internal review process or cede to the IRB of the University of Wisconsin. The study protocol was approved on July 24, 2018 and this manuscript reports on the most updated version of the protocol approved on October 19, 2020. All participant sites will be informed prior to enrollment that participation is completely voluntary, that they can withdraw from participation at any time, and that their decision to participate or not will not affect their health care in any way.

Upon completion of the study, we will present the results at major scientific conferences and will publish the results in peer-reviewed journals.

Author contributions

NS, PC, RB, AL, JO, and LS conceived of the study concept and design. VP drafted the overall protocol, with critical input from NS and RB for study design, recruitment, and statistical analysis. RB drafted protocol sections for statistical analyses; and PC for implementation

analysis. All authors provided critical feedback and approved the final version of the manuscript.

Competing Interests

None declared.

Funding statement

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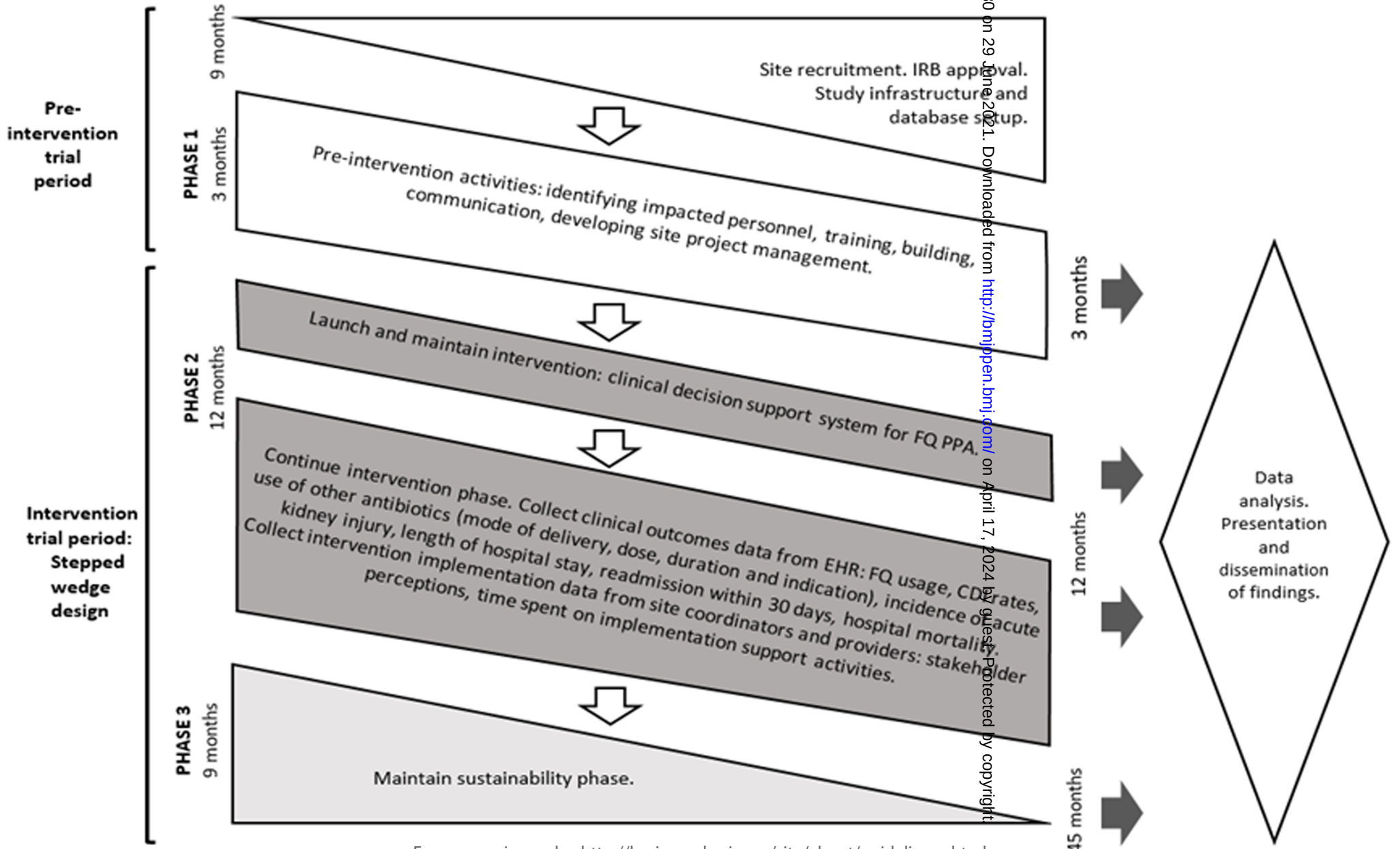

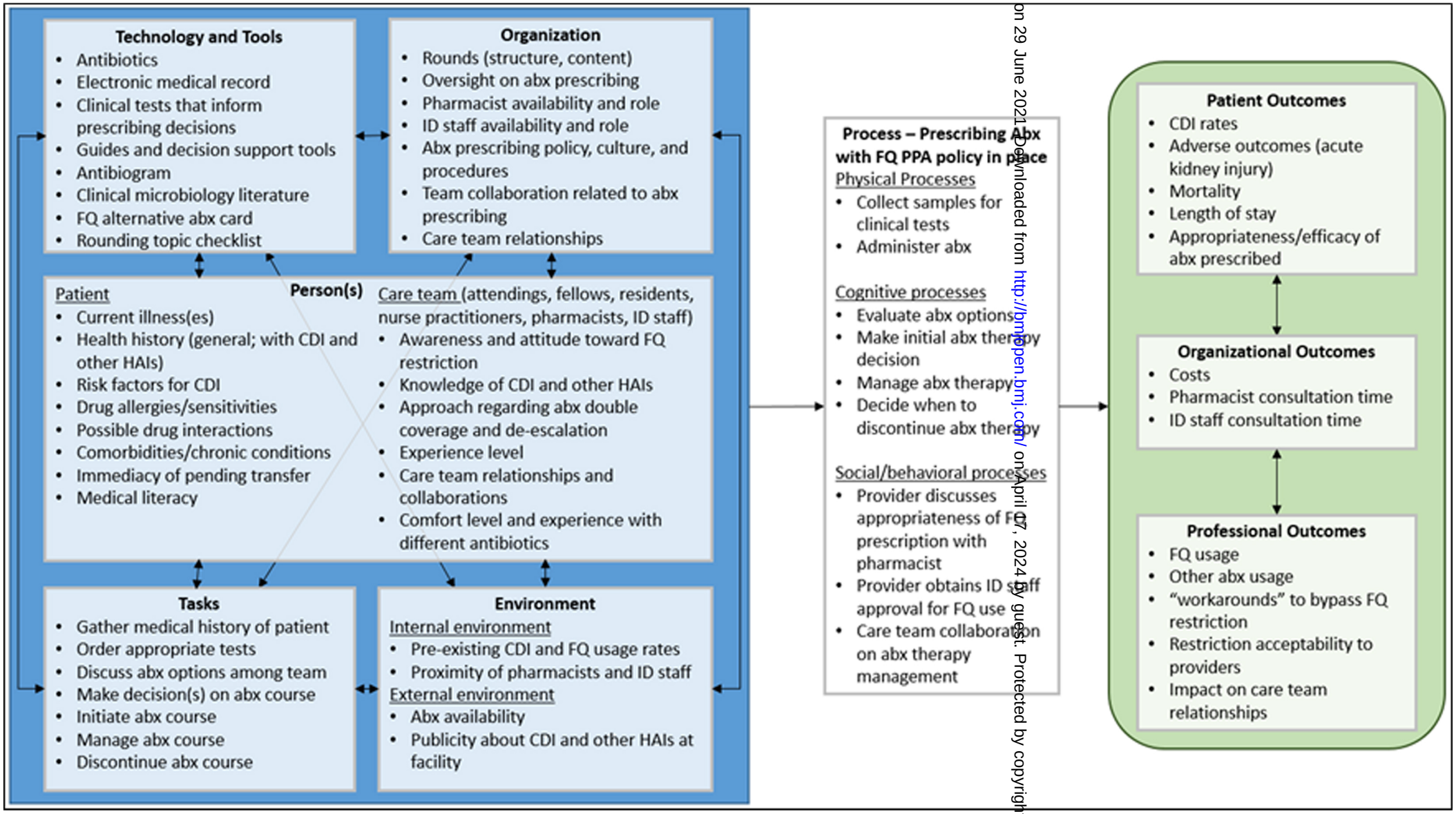

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	NCT03848689 at clinicaltrials.gov
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	23
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	10

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg,	6-7

		systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	19
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection,			

management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-24
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	26
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	26
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	26
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	26

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Notes:

- 2a: NCT03848689 at clinicaltrials.gov This checklist was completed on 30. October 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai