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Decreasing ICU-associated *Clostridioides difficile* infection through fluoroquinolone restriction, the FIRST trial: a study protocol

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ABSTRACT

Introduction *Clostridioides difficile* infection (CDI) is one of the most common healthcare-associated infections in the USA, having high incidence in intensive care units (ICU). Antibiotic use increases risk of CDI, with fluoroquinolones (FQs) particularly implicated. In healthcare settings, antibiotic stewardship (AS) and infection control interventions are effective in CDI control, but there is little evidence regarding the most effective AS interventions. Preprescription authorisation (PPA) restricting FQs is a potentially promising AS intervention to reduce CDI. The FQ Restriction for the Prevention of CDI (FIRST) trial will evaluate the effectiveness of an FQ PPA intervention in reducing CDI rates in adult ICUs compared with preintervention 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, using Epic as electronic health record (EHR) and pre-existing AS programmes. Sites will receive facilitated implementation support over the 15-month trial period, succeeded by 9 months of follow-up. The intervention comprises a clinical decision support system for FQ PPA, integrated into the site EHRs. Each ICU will be considered a single site and all ICU admissions included in the analysis. Clinical data will be extracted from EHRs throughout the trial and compared with the corresponding pretrial 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 number NCT03848689.

Strengths and limitations of this study

- The FIRST trial will provide one of the few national, multisite, comprehensive studies that investigate the effect on intensive care unit-associated *Clostridioides difficile* infection (CDI) of fluoroquinolone preprescription authorisation integrated as a computerised 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 intensive care unit-associated and hospital-associated CDI, providing more evidence for causality.
- Our approach simultaneously introduces antibiotic stewardship fluoroquinolone prescribing best practices and assesses the introduction of these practices, facilitating continuous implementation improvement.
- The primary limitation to this trial is a slowdown in recruitment rates with the SARS-CoV-2 COVID-19 pandemic and the uncertain effects of this pandemic on current intensive care unit sites.

INTRODUCTION

Background and rationale

Clostridioides difficile infection (CDI) is one of the most prevalent healthcare-associated infections in the USA[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 USA 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 use and overprescribing 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 the 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 preprescription authorisation (PPA) and post-prescription review and feedback.[15 16 22–34]

Of the antibiotic classes, fluoroquinolones (FQs) are one of the most frequently used 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 healthcare facility-onset CDI (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 HO-CDI cases nationally (30.7%).[3]

Study outcomes and measures

The trial described in this protocol is designed to implement an 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; however, implementation is often complex and variable between studies, making implementation evaluation difficult. We propose the integration of an 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 hypothesise that this FQ PPA intervention will result in decreased CDI rates during the intervention period and that quality improvement efforts will be enhanced by the University of Wisconsin-Madison 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 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 an 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 the STEWARDS (Structured Taskforce of Experts Working at Reliable Standards for Stewardship) panel recommendations, we will collect ICU-onset CDI rates as a subset of HO-CDI rates; HO-CDI rates; and healthcare-associated CDI (HA-CDI) rates as measures of trial effects.[42] We will also collect antibiotic utilisation 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 behavioural intervention using the SEIPS model.[41] SEIPS provides a broad and flexible way to characterise and evaluate work systems and care processes and the complex relationships among them using five work system elements: people, tools and technologies, tasks, organisational factors, and environmental factors.[43] This model will be used to characterise and evaluate the AS intervention and its impact on care processes and various patient, organisational 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 the clinical outcomes of the primary aim in a cross-case analysis.[45 48]

We used the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines in the preparation of this manuscript.[49]

Overall study design

A non-randomised, 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 1 is a 3-month pre-FQ PPA preparatory period for external facilitation of the implementation, prescriber education, building the FQ PPA CDS best practices alert (BPA), and early contextual and implementation data collection. Phase 2 is the 12-month intervention period during which the FQ PPA-BPA goes live, over which time

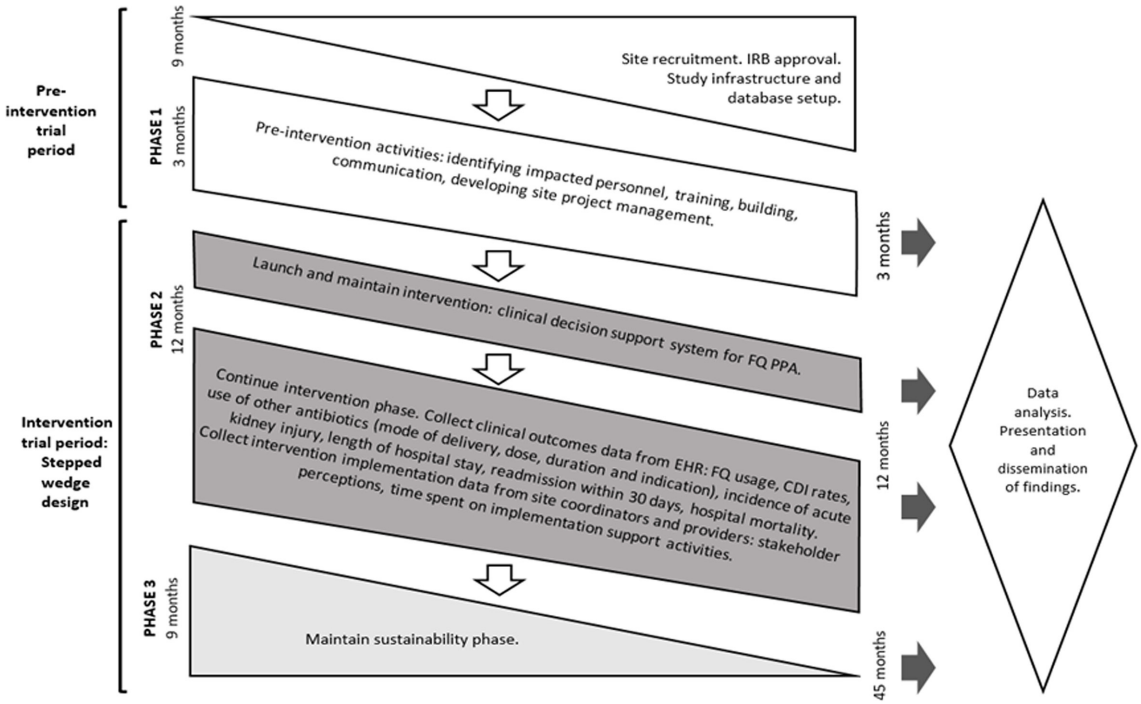

Figure 1 Schematic depiction of the trial design and procedures. CDI, *Clostridioides difficile* infection; EHR, electronic health record; FQ, fluoroquinolone; IRB, Institutional Review Board; PPA, preprescription authorisation.

both routinely collected clinical EHR data and implementation data will be regularly collected. Phase 3 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 preintervention period will constitute the baseline for comparison with the phase 2 intervention period. The influences on 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.

Trial organisation

Steering committee

The steering committee (SC) will be chaired by the principal investigator (NS) and include the lead biostatistician (RB), coinvestigators (PC, LS, Aurora Pop-Vicas) and other study personnel (VP, AL, 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.

Data coordinating centre

The data coordinating centre (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 at the University of Wisconsin-Madison, led by the study biostatistician (RB) and the data manager (Fauzia Osman). The University of Wisconsin-Madison team will be responsible for oversight of the DCC activities.

Clinical coordinating centre

The clinical coordinating centre (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 Agency for Healthcare Research and Quality (AHRQ). The CCC will be physically located at the University of Wisconsin-Madison and led by the principal investigator (NS) and study lead (VP).

Data collection and management

The electronic case report forms (eCRFs) will be finalised 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 data set and site personnel will have access to site-specific data.

Site monitoring

We are planning site virtual initiation visits prior to site enrolment. 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 AS 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 optimise adherence to established AS best practices, real-time AE monitoring was not considered necessary. Once the study is in place, an independent, ad-hoc drug safety and monitoring board 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 University of Wisconsin study team for review.

Patient and public involvement

The University of Wisconsin team has consistently worked with a patient stakeholder group, the Patients Engaged in Education and Research 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 AS 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 programme with pharmacist and infectious disease physician support and with Epic Systems Corporation as their EHR vendor. Their EHR must have the ability to extract antibiotic usage data (DOT), 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 risk of CDI. These criteria were selected so that the intervention could be implemented in a standardised 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 University of Wisconsin 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 the 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 the 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 pretrial 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 an 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 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 an 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]

Usual care

Usual care for this trial will include no active restrictions to FQ use. Sites may still choose to use postprescription feedback for FQ if that is their usual practice. There may be restrictions to other antibiotics as per a site's usual

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, 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, an 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 analyse 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.

AS, antibiotic stewardship; CDI, *Clostridioides difficile* infection; FQ, fluoroquinolone; ICU, intensive care unit; ID, infectious disease; PPA, preprescription authorisation.

practice and an active AS programme 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 standardised 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 2 intervention period and the corresponding 12-month preintervention 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) healthcare-associated infections 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.

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 an NR-SW cluster design, we will need monthly assessments, CDI 12 months preintervention and 12 months postintervention, 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[56] 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 programme intervention level and trend change.

Multiple ICU units (12 ICUs) will be nested in five hospitals. This would typically provide a very small number of units to be modelled 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.

Table 2 Variables to be collected for aim 1 analysis

Unit-level (or hospital-level) variables	Type of variable	Operational definition	How data are extracted
Healthcare facility-onset CDI with ICU onset	Primary outcome	Positive test for CDI from ICU specimen sent from a symptomatic patient on or after day 4 of admission to healthcare facility.[63]	Routinely collected by infection control.
Healthcare facility-onset CDI	Primary outcome	Positive test for CDI from a symptomatic patient on or after day 4 of admission to healthcare facility.[63]	Routinely collected by infection control.
Healthcare-associated 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	DOT per patient admission and DOT per 1000 PD*.	EHR—routinely collected by AS.
All other antibiotic usage	Secondary outcome	DOT per patient admission and DOT per 1000 PD*.	EHR—routinely collected by AS.
AKI	Secondary outcome	KDIGO guideline definition.[64]†	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 North American pulsed-field gel electrophoresis type 1 (NAP1) strain 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‡.	Extracted from EHR.
Ethnicity	Descriptive	Hispanic or Latino; not Hispanic or Latino‡.	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§.	Chart review of a sample of cases.

Continued

Table 2 Continued

Unit-level (or hospital-level) variables	Type of variable	Operational definition	How data are extracted
Historical factors	Descriptive	Historical factors that may influence findings.	Infection control and AS data.
SARS-CoV-2 (COVID-19) infection status	Descriptive	Positive/negative status.	Extracted from EHR.

*A single DOT will be recorded for each individual antibiotic administered to a patient on a given day. Antibiotic use will be normalised to patients' DOT per 1000 PD as well as per patient admission.
†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]
‡These categories are consistent with the US Office of Management and Budget (OMB) 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]
§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 endeavour, we will focus on sepsis treatment.
AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; AS, antibiotic stewardship; CDI, *Clostridioides difficile* infection; DOT, days of therapy; EHR, electronic health record; FQ, fluoroquinolone; HAI, healthcare-associated infection; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; PD, patient-days.

We will use two analytic strategies, the first being a multilevel logit random effects model on the incidence of CDI in all ICU sites, following procedures suggested by Huynh *et al*'s[50] simulation for analysis of NR-SW designs. All models will be constructed using MLwiN V.3.02 software.[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 preintervention and 12-month postintervention 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 programme, we propose regression discontinuity analysis using an autoregressive regression model. All interrupted time series models will be constructed using Stata's V.14 routine interrupted time series analysis.[59]

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-19 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 1 and 2, 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 Institutional Review Board-approved surveys, semistructured interviews 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.

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 60] 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).

The concurrent implementation of the FQ intervention and evaluation of its impact corresponds to the convergent parallel trial design in mixed-methods research[46 47 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 the 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 *et al*.[48] We will use a systematic comparative pattern analysis method to iteratively compare and emphasise 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.[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.

Table 3 Implementation data sources and analysis

Domain	Instrument	Components	Outcome measures
Contextual site information	Site infection prevention practices	Infection prevention programme, 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; presurgical decolonisation procedures and surgical targets; contact precautions by organism; hand hygiene procedures, compliance and feedback; personal protective equipment 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 procedures; preprescription programme procedures; audit and feedback specifications and process; antibiotic utilisation monitoring; antibiotic consumption monitoring and reports; antibiotic susceptibility testing; antibiogram data.	Contextual information for cross-site comparison; implementation analysis.
	ICU information	ICU facility type and model; number of beds; ICU critical statistics (average 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-implementation and post implementation related activities, participants and durations.	Implementation analysis: timeline.
	Site startup activities	Identification of site contacts and implementation roles; preintervention support and task status.	Implementation analysis: timeline.
	Check-in meeting notes	Record of changes to sites' AS or infection prevention (IP) practices; barriers to and facilitators of introducing intervention.	Implementation analysis: barriers and facilitators.
	Usability test	Prelaunch 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.
	Semistructured 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 and 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.

AS, antibiotic stewardship; BPA, best practices alert; EHR, electronic health record; FQ, fluoroquinolone; HAI, healthcare-associated infection; ICU, intensive care unit; PPA, preprescription authorisation.

The triangulation with multiple analysts will enhance the quality of the analysis and ensure its rigour.[61 62]

DISCUSSION

We expect this study to demonstrate that the FQ PPA intervention results in a decrease in FQ usage in ICU settings and lowers 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

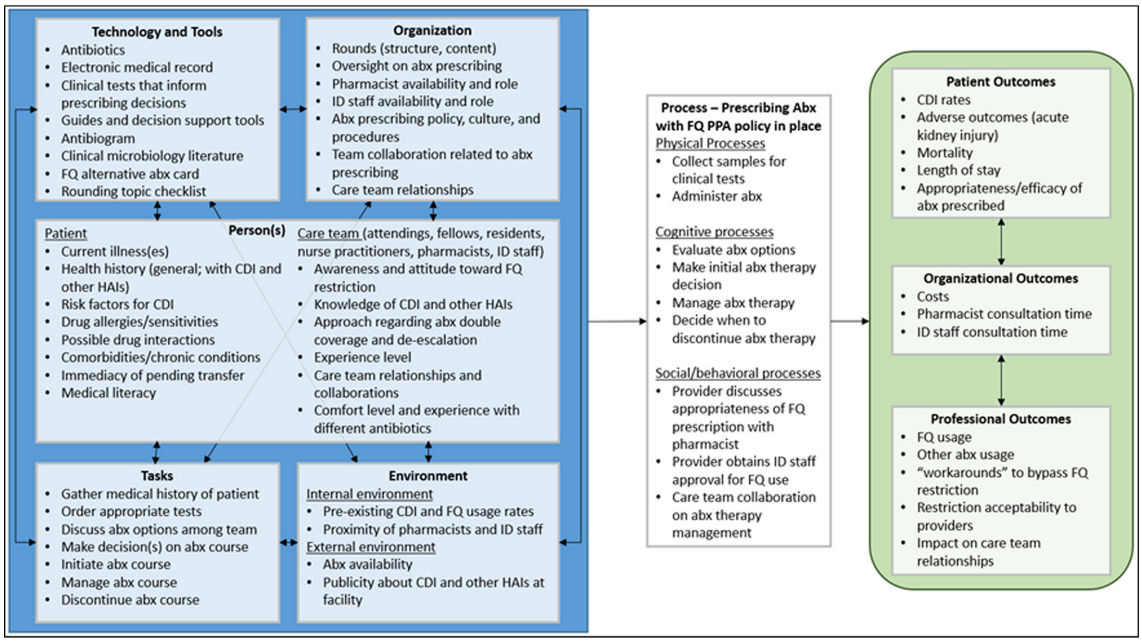

Figure 2 SEIPS framework: FQ PPA implementation in acute care settings. Abx, antibiotics; CDI, *Clostridioides difficile* infection; FQ, fluoroquinolone; HAI, healthcare-associated infection; ID, infectious disease; PPA, preprescription authorisation; SEIPS, Systems Engineering Initiative for Patient Safety.

PPA in acute care settings and improve the quality of AS programmes 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 the 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 the results of this trial. Among 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 Institutional Review Board of the University of Wisconsin. The study protocol was approved on 24 July 2018 and this manuscript reports on the most updated version of the protocol approved on 19 October 2020. All participant sites will be informed prior to enrolment 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 healthcare in any way.

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

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