The INSPIRE-ASP Trial (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients) for Abdominal (ABD) Infections Protocol

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Brief Overview

The **INSPIRE-ASP Trial** (**IN**telligent **S**tewardship **P**rompts to **I**mprove **R**eal-time **E**mpiric **A**ntibiotic **S**election for **P**atients) **for Abdominal (ABD) Infections** is a cluster-randomized trial of 92 hospital randomized units (102 individual hospitals)to improve physicians' choice of antibiotics for patients hospitalized with ABD infections by reducing the unnecessary use of extended-spectrum antibiotics. This trial provides prescribers in half the hospitals with prescribing advice based on the probability that a patient is infected with antibiotic resistant bacteria. Provision of unnecessary extended-spectrum antibiotics carry risks, and the goal of this trial is to limit their use to situations in which the patient is likely to require them, while maintaining excellent patient outcomes.

We hypothesize that providing clinicians with individual patient risk estimates for antibiotic-resistant infections will reduce the overuse of empiric extended-spectrum antibiotics among patients hospitalized for ABD infections. To do this, we will use patient information in the electronic health record plus local hospital laboratory data on antibiotic resistance in ABD cultures to develop an automated smart tool that provides the likelihood that a patient needs extended-spectrum antibiotics. 102 hospitals were randomized into 92 hospital units, into either routine care (46 hospital units) or to the intervention arm (46 hospital units) receiving the INSPIRE Stewardship Bundle which includes CPOE smart prompts, clinician feedback reports, and activities to support CPOE adoption (e.g., education and modifications of CPOE workflows as needed). In half of these hospitals, physicians will be prompted to use standard-spectrum antibiotics when the risk of antibiotic-resistant infection is low. This 12-month intervention will evaluate approximately 99,000 patients with ABD infections.

Protocol Summary

This protocol provides detailed instructions for the conduct of the INSPIRE-ASP Trial (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients) for Abdominal (ABD) Infections. This trial is a 92 hospital unit (102 individual hospitals), 99,000 patient cluster-randomized trial to improve physicians' choice of antibiotics for hospitalized patients by reducing the unnecessary use of extended-spectrum antibiotics while maintaining excellent patient outcomes. This trial will be conducted in the HCA Healthcare system, which provides 5% of acute care services in the United States.

Hospitals will be recruited through usual HCA Healthcare communication channels and randomized into a two-arm trial involving routine care or routine care plus a stewardship bundle that includes real-time personalized risk calculator for whether a patient with ABD infection is infected with an antibiotic-resistant pathogen warranting extended-spectrum antibiotic therapy. This protocol details eligibility criteria for participation, factors accounted for in 1:1 hospital randomization, notification of randomization assignment, and provision of the two arms with arm-specific toolkit information and coaching calls. It also details the process by which centralized IRB approval and reliance agreements will be obtained.

This trial evaluates a quality improvement antibiotic stewardship strategy, the INSPIRE Stewardship Bundle, that includes (1) computerized physician order entry (CPOE) decision support alert that provides physicians with patient-specific risk estimates for having a (ABD) infection due to a multidrug-resistant organism (MDRO) and recommends standard spectrum antibiotics for low risk patients in the first 3 days of hospitalization; (2) clinician feedback reports, and (3) activities to support CPOE adoption (including education and alignment of CPOE workflows). As such, all implementation will be performed through the local infrastructure provided by hospital antibiotic stewardship program leaders who serve as study champions. Participating hospitals in both arms will approve the arm-specific study protocol through usual hospital committees. The routine care arm will participate in regular coaching calls to ensure best practice for national standards of stewardship are taught and encouraged. This arm will also launch trial-specific modifications to the existing antibiotic indication screens.

Several activities are detailed for the INSPIRE Stewardship Bundle arm. These include pre-launch activities such as participation in coaching calls and an on-site training visit, as well as procedures to locally install corporate MediTech software for the CPOE personalized risk calculator for ABD infection antibiotic indications, including any modifications needed to align the CPOE workflow to support the INSPIRE prompts (e.g., order-based exclusion of ICU patients, order set changes). In addition, the sites receiving the INSPIRE Stewardship Bundle will receive educational materials, participate in monthly coaching calls and every other month check in calls, and receive clinician audit reports to feedback to physicians and hospital leadership about protocol adherence.

As a pragmatic trial, all data will be obtained from the HCA Healthcare centralized clinical data warehouse. Local site champions will not need to collect any outcome data or variables for description or adjustment. This protocol describes how data will be obtained through a data use agreement between HCA Healthcare and Harvard Pilgrim Health Care Institute (data and analytic center for the trial). Data and programmer analysts will access and analyze data on the HCA Healthcare server behind the HCA Healthcare firewall, thus ensuring maximum data protection.

In summary, the INSPIRE Trial for Abdominal (ABD) Infections is a randomized trial of 92 hospital units (102 individual hospitals) and approximately 60,000 patients to improve physicians' choice of antibiotics for patients hospitalized with abdominal infection by reducing the unnecessary use of extended-spectrum antibiotics. This protocol provides the road map for the conduct of the trial to determine if a personalized real-time risk calculator plus audit and feedback can improve judicious use of antibiotics in hospitalized patients.

B. Background Information and Scientific Rationale

B.1. Background Information

National Call for Antibiotic Stewardship in an Era of Antibiotic Resistance

Inappropriate use of extended-spectrum antibiotics is a major driver of the 2 million antibiotic-resistant infections in the U.S. each year.[1,2] Nearly 40% of inpatient antibiotics are inappropriate or unnecessary.[3,4] Unfortunately, rising antibiotic resistance has fueled rather than curbed extended-spectrum antibiotic use, with prescribers using extended-spectrum agents for the possibility of resistance, thus leading to a detrimental cycle that urgently needs attention.[5]

A main principle for judicious prescribing is to use the narrowest spectrum antibiotics necessary to treat infection. Antibiotics that cover the vast majority of organisms that cause a particular disease are "standard-spectrum" agents, with "extended-spectrum" agents reserved for infections proven to be caused by antibiotic resistant organisms not covered by standard-spectrum agents, or for critically ill patients for whom there may not be time to wait for culture and susceptibility results. However, many U.S. clinicians routinely use extended-spectrum antibiotics empirically to cover rare events.

B.2. Rationale

In 2015, in response to a dwindling antibiotic arsenal active against resistant bacteria, a U.S. national action plan was forged.[6] It called for every hospital to implement an antibiotic stewardship program with a set of core elements. Current stewardship programs employ a variety of unproven and labor-intensive approaches to promote judicious antibiotic prescribing. Pragmatic clinical trials to identify best practice are needed.[7]

Abdominal Infections (ABD) Infections as Critical Disease Targets

ABD infections are responsible for over a million hospitalizations each year, and data from 140 hospitals suggest that 52% of ABD infections are treated with an empiric extended-spectrum antibiotic intended to treat MRSA, *Pseudomonas*, or multidrug-resistant Gram-negative rods (MDR GNR) although the frequency of these pathogens is only 4.2%.[8-11] Publications have highlighted the inordinate use of unnecessary extended-spectrum antibiotics in ABD infections.[12,13] Guidelines from the Infectious Diseases Society of America (IDSA) for mild-moderate disease (e.g. non-critically ill patients) gives wide latitude in choice of empiric antibiotic, while urging restraint to avoid antipseudomonal and MRSA coverage unless local resistance is 10-20%.[14] We will address the excessive use of extended-spectrum antibiotics for ABD infections by considering the actual risk of antibiotic resistant bacteria requiring those antibiotics.

Rationale for Intervention Strategy
Scientific Basis and Clinical Significance

Rising antibiotic resistance and the slow development of novel antibiotics have fueled national calls to improve antibiotic choices by frontline physicians. There is a 2020 target to reduce "inappropriate" antibiotic prescribing in hospitals by 20%, as discussed in the 2014 "National Strategy for Combating Antibiotic-Resistant Bacteria" released by the White House. While physicians agree that antibiotics are overprescribed, most fail to recognize areas for self-improvement. Therefore, hospitals have been charged with developing antimicrobial

stewardship programs which provide ongoing education and feedback to physicians and ensure accountability in prescribing. Many patients who are prescribed antibiotics in U.S. hospitals receive inappropriately extended-spectrum antibiotics. A major driver of unnecessary broad-spectrum antibiotic use is clinicians' overestimation of the likelihood that the patient is infected by a multidrug-resistant organism (MDROs). To improve the success of these efforts, it is critical to develop evidence about best practices for improving judicious antibiotic prescribing. Evidence, engagement, and education are required to build a culture where it is accepted that rationale antibiotic prescribing is every physician's responsibility.

The current focus of U.S. antimicrobial stewardship efforts has been to establish local hospital programs outfitted with a multi-disciplinary team of clinicians and pharmacists. National recommendations involve reviewing the antimicrobial formulary, and ensuring appropriate weight-based dosing, and IV vs oral selection. In recent years, national recommendations have targeted clinical care optimization by recommending processes to establish and update local antibiograms, evidence-based treatment guidelines and order sets, and active review of antimicrobial therapy to narrow antibiotic choice when pathogens grow from clinical cultures – e.g. "de-escalation" after when clinical cultures yield pathogens, generally three to seven days after cultures are sent.

These efforts, while admirable, do not address the majority of inappropriate antibiotic use in hospital settings, because the majority of antibiotics are prescribed empirically while pending any possible knowledge of the causative pathogen from clinical cultures. Culture results and antibiotic susceptibilities typically become available at or after the third hospital day, which is also the median duration of hospital stays. Therefore, the target for de-escalation is modest, compared to the substantial use of empiric therapy, which is often initiated in emergency rooms.

Analysis of the Need and Impact on Healthcare

Abdominal (ABD) infections are among the most common infectious reasons for hospitalization. ABD infections are responsible for over a million hospitalizations each year and HCA Healthcare data from 140 hospitals suggest that over 80% of ABD infections are treated with an empiric regimen that includes an extended-spectrum antibiotic intended to treat MRSA, *Pseudomonas*, or multidrug-resistant *Enterobacterales*. Nevertheless, estimates of the frequency of these pathogens is only 2%; thus, showcasing the inordinate unnecessary use of extended-spectrum antibiotics.

While there is an appropriate focus on rapid initiation of extended-spectrum antibiotics for patients who are septic or require critical care, there is a need to focus on use of standard spectrum empiric antibiotic regiments for the much larger population of patients who require hospitalization, but are not critically ill, and who are at low risk of MDR pathogens.

B.2.1 Innovations in Implementation

This trial evaluates a novel strategy that interfaces with prescribers in real time to provide a) a patient- and hospital-specific probability that the patient is infected with an antibiotic-resistant pathogen, and b) a recommendation to use standard spectrum empiric therapy if the risk is below a threshold determined in consultation with clinical experts and HCA Healthcare leaders. This strategy is novel for two reasons. It targets **empiric antibiotic prescribing** with the intent of influencing a physician's initial choice of antibiotics. Second, it provides **precision-medicine estimates of MDRO infection risk** based upon the local antibiogram and an individual patient's specific characteristics in the electronic health record.

B.2.2 Innovations in Intervention

Our trial intervention offers six innovations. **First,** the INSPIRE-ASP Trials uniquely focus on empiric antibiotic selection when most stewardship programs focus on de-escalation. Targeting empiric prescribing has greater impact potential because it acts earlier in the prescribing sequence and because most physicians are reluctant to change a decision made by a prior physician.[23] **Second,** this trial creates a computer provider order entry intervention that dually reaches emergency department and hospital-based physicians for patients being admitted. **Third,** this trial re-engineers the antibiogram, providing syndrome-based risks of antibiotic

resistance instead of pathogen-based risks. This improves the relevance for physicians as they treat abdominal pain and reduces misinterpretation (see **Section 1.2**). This trial mines the electronic health record for patient and hospital characteristics associated with antibiotic-resistance and returns a highly curated risk estimate on whether an individual patient needs the extended-spectrum antibiotic that the physician is attempting to prescribe. This would be the first cluster-randomized trial of a precision medicine risk calculator for ABD infection. **Fourth,** this trial trains physicians to focus on absolute vs relative risk. Most papers and guidelines provide relative risks instead of absolute risks that risk factors confer for an outcome. As an example, a large study found that peripheral vascular disease confers a 5-fold risk of MRSA carriage.[24] Because 5-fold is a large ratio, this can be misinterpreted to mean that all patients with peripheral vascular disease should be treated as if they harbor MRSA. In actuality, the 5-fold risk reflects a carriage risk of 2.4% among those with peripheral vascular disease vs 0.5% in those who do not.[24] Both risks are small. In this trial, we assess a host of risk factors relevant to whether a patient is infected with an organism resistant to the antibiotic that the physician is prescribing. When the risk factors collectively generate a low (e.g., <10%) risk, we prompt the physician to replace an in-progress order for an extended-spectrum antibiotic with a standard spectrum agent. **Fifth,** this trial works to change the notion that the physician is "wrong" if their actions do not match what eventually grows from a culture. We should not expect physicians to be prescient. Instead, we should expect physicians to make a decision that best accounts for the available evidence. This trial documents the presence of risk factors and the calculated risk in the electronic medical record and establishes antibiotic stewardship protocols that promote certain actions at specific risk estimates. This allows "right" decisions to be based on reasonable probabilities and thus reduces "just in case" prescribing. **Sixth,** while the main goal of the trial will be to reduce unnecessary extended-spectrum antibiotic prescribing when the calculated need is low, we will also explore the impact of prompting physicians to order extended-spectrum antibiotics when the calculated risk is high and physicians order standard-spectrum agents.

B.3. Potential Risks and Benefits

B.3.1. Potential Risks

Minimal Risk

This trial involves a minimal risk strategy of providing physicians with information from a risk calculator designed to assess the risk of having an antibiotic-resistant infection based upon patient and hospital characteristics.

Reasons supporting a minimum risk determination include:

1) The intervention, INSPIRE Stewardship Bundle, is a quality improvement program and does not involve direct testing of any FDA regulated product
2) The participants are hospital antibiotic stewardship programs, not individual patients
3) The protocol is concordant with current national guidelines for antibiotic prescribing,
3) The intervention involves computerized provider order entry (CPOE) prompts that provide risk estimates and recommendations, but does not supplant clinical judgment (physicians maintain final decision-making autonomy for antibiotic prescribing at all times),
4) Evidence suggests that there is time to wait for culture results in non-ICU patients instead of using empiric extended-spectrum antibiotics for uncommon resistant organisms.

The primary risk in this study is to patient privacy and confidentiality of study data, for which we have ample protections (see below)

B.3.2 Known Potential Benefits of the Proposed Research to Human Subjects and Others

This study has potential benefits at the individual, hospital, and societal level. For individual participants in the Intervention Arm, this study has the potential to reduce unnecessary antibiotic use, possibly preventing adverse events such as emergence of resistant pathogens, adverse kidney effects, and antibiotic-associated diarrhea. Importantly, reduction in these outcomes would have broader benefits on hospital bacteria as well as economic impacts to the hospital and society for both costs of unnecessary antibiotics and cost of infections due to engendered antibiotic resistance.

C. Objectives

The objective of this protocol is to provide direction for the conduct the INSPIRE-ASP Trial for Abdominal (ABD) infections. This trial will compare routine care vs a real-time precision medicine needs assessment for extended-spectrum empiric antibiotics in a 92-hospital unit (102 individual hospitals), cluster-randomized trial.

This protocol will:

- Describe the INSPIRE Stewardship Bundle
- Provide details of the personalized risk calculator for determining the likelihood of resistant organisms
- Provide information on how to install the computerized physician order entry (CPOE) risk calculator into your local Meditech system
- Detail the toolkit that you will receive for intervention guidance
- Describe the feedback and audit reports

D. Study Design and Population

Title: The INSPIRE-ASP Trial (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients) for Abdominal (ABD) Infections.

Study Design: Cluster-randomized trial

Participant: 102 Hospitals affiliated with HCA Healthcare randomized into 92 units. Hospitals with shared antibiotic stewardship teams (physicians or pharmacists) are randomized together as a single hospital unit. Inclusion criteria includes affiliation with HCA Healthcare and use of Meditech (for standardized build of CPOE prompts for the INSPIRE Stewardship Bundle arm). Any qualifying facility wishing to participate will be permitted to enroll even if in excess of calculated study sample size to accommodate HCA Healthcare facility or division-level antibiotic stewardship goals. Exclusion criteria include care of <100 ABD infection patients per year, and implementation or planned implementation of a new antibiotic stewardship intervention directly conflicting with the trial in the baseline or intervention period.

Population: The analytic cohort will be patients with ABD infection. Inclusion criteria include adults ≥18 years old admitted to a general medical or surgical floor (non-ICU) of a participating HCA Healthcare hospital with a diagnosis of ABD infection. In addition, patients must receive a systemic antibiotic in the first 3 days of hospitalization (empiric period). Exclusion criteria will include age <18 years old and ICU admission on either hospital day 1 or 2. Hospitals that do not use Meditech are excluded from participation, as are those who use/will use Meditech Expanse or Patient Keeper for order entry.

Number of Sites: 92 HCA Healthcare hospital units (102 individual hospitals)

Study Duration: 5-month phase-in period (does not contribute to analysis) and 12-month intervention period

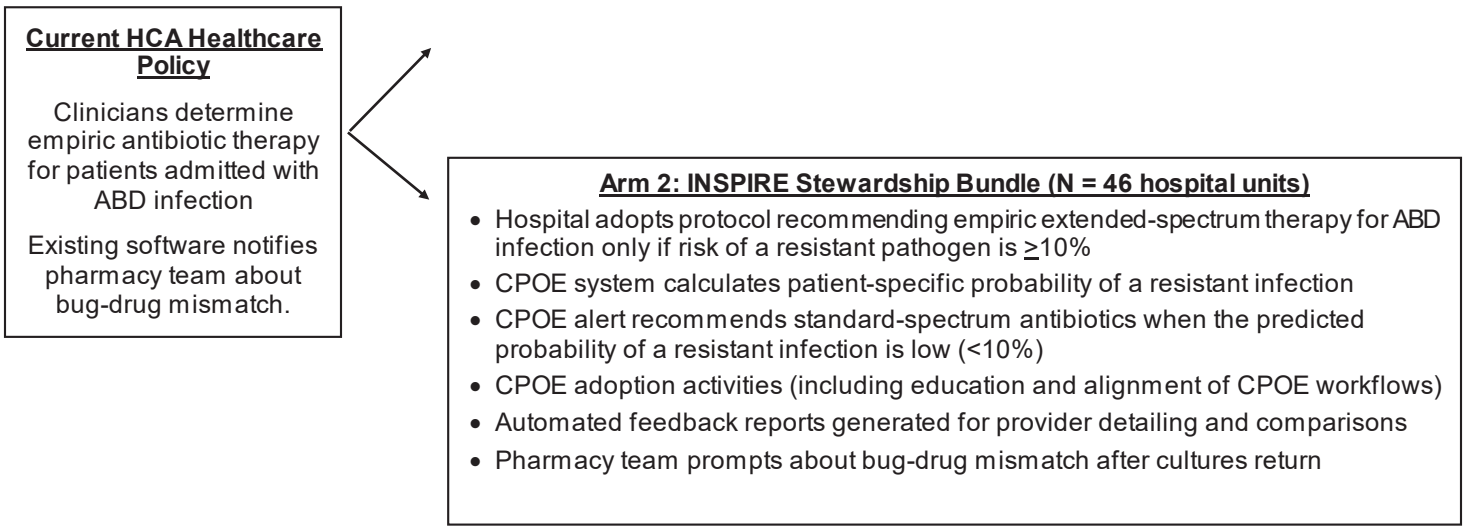
Subject Duration: Eligible hospital admission

Schematic of Study Design:

Figure 1: **Two Study Arms of the INSPIRE-ASP Trial**

Arm 1: Routine Care (N = 46 hospital units)

- Routine prescribing practice for ABD
- Pharmacy team prompts about bug-drug mismatch after cultures return



E. Study Procedures

E.1. Randomization

Randomization will occur in the first quarter of the second year of the study. Hospitals will be notified of their randomization results via a formal email to each facility's study champions as well as to the Chief Medical Officer, Chief Executive Officer, Pharmacy Director, and IT&S Director. A separate coaching call for each arm will be scheduled following randomization notification to provide the facilities with the next steps in the trial. Following randomization, all subsequent coaching calls, toolkit binders, FAQs, and help line contact groups will differ by arm assignment.

E.2. Intervention

E.2.1 Phase-In Period Activities

Post-Randomization Committee Approval and Software Implementation for Antibiotic Indication Screens

- **Arm 1:** Facilities randomized to the control arm, which will not receive the antibiotic stewardship quality improvement intervention, the INSPIRE Stewardship Bundle, still need to undergo usual hospital approval by relevant committees to participate in the trial. The committee process will be dependent on local hospital operations, but is anticipated to include the antibiotic stewardship subcommittee, pharmacy and therapeutics committee, and medical executive committee. Determination of the committees from which to seek approval is the purview of the participating hospital. The INSPIRE study coordinators will request that each site provide the list of requisite committees for approval and convening dates for each committee. A tracker will be maintained to ensure all requisite committee approvals have been received.

  In addition, although Arm 1 facilities will not receive the personalized risk prediction algorithm, they will be required to install a CPOE software modification for antibiotic indication screens similar to Arm 2. Currently, all providers ordering an antibiotic are required to input an indication for the antibiotic. This antibiotic indication screen will be modified to allow more clarity to systemic indications such as "sepsis." For example, if providers select "sepsis," a second screen will appear asking the provider if the source of the sepsis is ABD infection; similar approaches will be taken if providers choose "empiric" or "other". This programming can be readily adapted from a previous trial for pneumonia and urinary tract infection that already created such a subprompt for sepsis. This will be installed for both arms so that data on indications for prescribed antibiotics can be compared between the two arms. Both arms will also receive a prompt asking if patients with ABD infection indications are likely to be admitted to an ICU (an exclusion criterion).

- **Arm 2:** Facilities randomized to receive the intervention (antibiotic stewardship quality improvement intervention, the INSPIRE Stewardship Bundle, to be implemented via usual care processes including order sets and prompts within the electronic medical record) will need to undergo hospital approval by relevant committees. The committee process will be dependent on local hospital operations, but is anticipated to include the antibiotic stewardship subcommittee, pharmacy and therapeutics committee, and medical executive committee. Determination of the committees from which to seek approval is the purview of the participating hospital. The INSPIRE study coordinators will request that each site provide the list of requisite committees for approval and convening dates for each committee. A tracker will be maintained to ensure all requisite committee approvals have been received.

  In addition, Arm 2 facilities will receive a software modification for antibiotic indication screens as described for Arm 1. They will also receive a CPOE software modification from corporate HCA Healthcare information technology to install the risk prediction algorithm (see below).

Site-Visits

Following randomization, site visits to Arm 2 (INSPIRE Stewardship Bundle) facilities will be conducted by the INSPIRE study investigators and an HCA Healthcare corporate pharmacy liaison. Study investigators will visit participating facilities either on-site or virtually to engage site leadership and key stakeholders, provide an overview of the trial and intervention activities, review roles, responsibilities, expectations of Study Champions and ASP leaders, and review plans for education and prescriber feedback for site clinicians. Site visits will be scheduled following randomization notification, both prior and during the launch of the phase-in period of the trial. Requested local participants will include Study Champion, stewardship pharmacy and clinician champions, hospital leadership, ED clinician leads, hospitalist clinician leads and any other key stakeholders identified by the local Antibiotic Stewardship Program. Repeat post-launch site visits for facilities that need additional support throughout the trial will also be available as needed or requested.

Pre-launch Coaching Calls

Coaching calls will be held for both routine and intervention facilities during the pre-launch and phase-in periods. Coaching call reminders will be sent one week and one day prior to the call. This communication will include the list of polling questions, so that participants have time to prepare for answering these questions as accurately as possible. These web-based coaching calls during the pre-launch and phase-in periods will be held to build engagement and review upcoming activities. These calls will be scheduled at least 3 weeks ahead of time to ensure Study Champions, Antibiotic Stewardship Pharmacy and Clinician Champions, and any other requisite local stakeholders can attend. The end of each coaching call will include a series of polling questions to understand facility-level implementation progress, feedback and education.

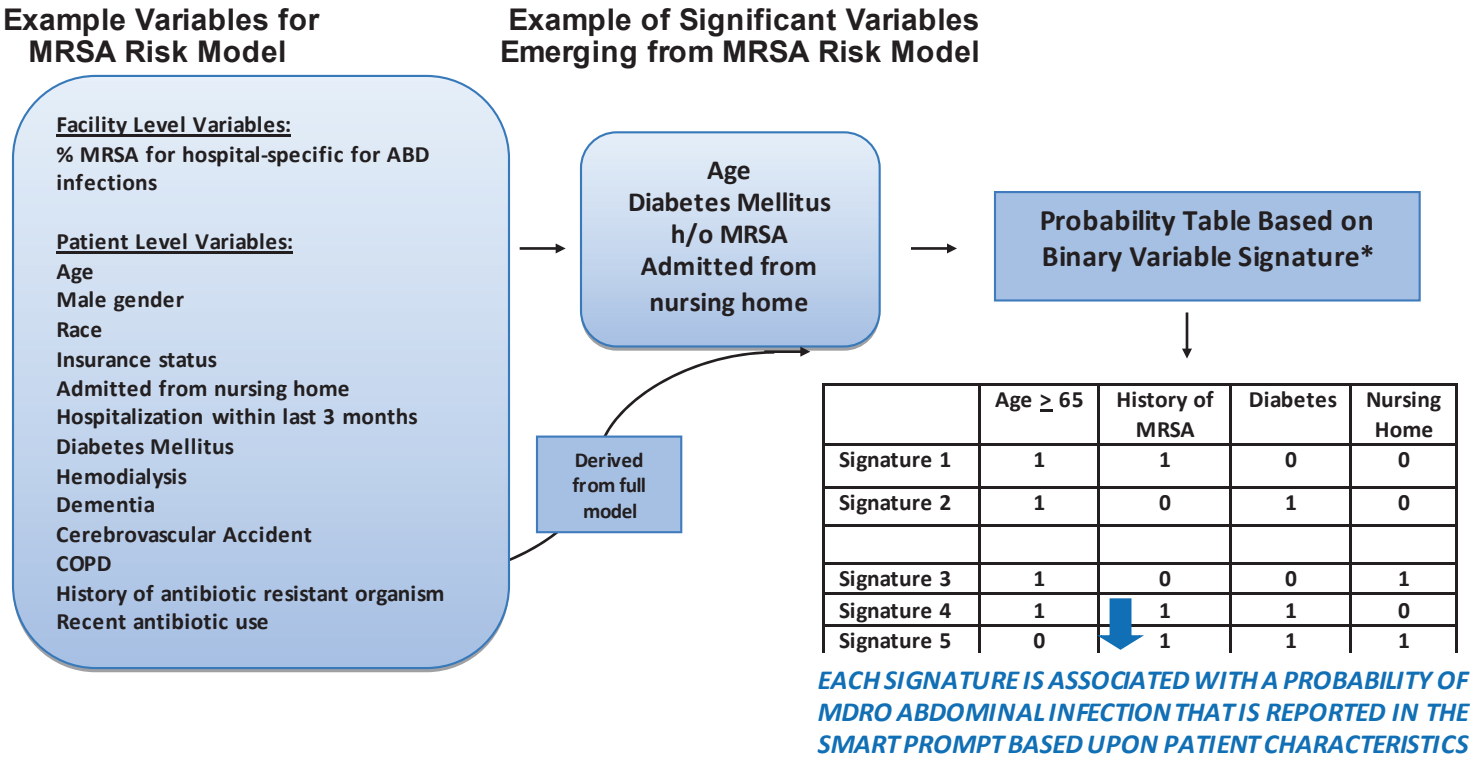
The call-in system is very sophisticated and highly regulated. It logs participant names and allows posting of real-time polling questions. Hospitals that are not represented on coaching calls will receive an email from study staff and a phone call from HCA Healthcare trial liaisons (if needed) to address inquiries raised on the coaching calls and ensure future active participation.

How the Risk Estimator Works

Using a personalized set of risk estimates based upon patient characteristics and local antibiotic resistance data, we will predict the need for extended-spectrum antibiotics in patients with ABD infections. These characteristics discriminate between high and low risk patients and generate absolute risks to guide clinician therapy instead of relative risks which are commonly found in medical literature.

Coaching calls in the pre-launch and phase-in periods will review the risk calculator and the characteristics that best determine antibiotic risk (Figure 2).

Figure 2. Example Development of Automated Precision Medicine Smart Tool Providing MRSA Risk Estimates for Patients Admitted with Abdominal (ABD) Infections



The corporate HCA Healthcare Information Technology (IT) team will develop the CPOE Personalized Risk Estimate Prompt template which will include creation of smart prompt algorithms, automated compliance reports, and centralized beta testing. Installation processes, modifications of CPOE workflow to accommodate the INSPIRE CPOE prompt, educational materials, and training modules will be developed as described below.

CPOE Prompt Installation

Following the development of the CPOE Personalized Risk Estimate Prompt by the corporate HCA Healthcare Information Technology (IT) team, the software will be pushed out electronically to all intervention facilities. The local IT groups will then install and integrate the CPOE Personalized Risk Estimate Prompt into their local MEDITECH system. The risk prompt functionality will be installed in all Emergency Departments and non-ICU locations within the facilities. Following the installation process, a testing process at each facility involving the antibiotic stewardship team will ensure the following:

- The risk estimate prompt functions accurately for abdominal (ABD) infections. For example, when physicians order an antibiotic of interest, they will be required to enter the indication for the antibiotic. For indications of ABD infections, the risk estimate prompt will return the probability that the antibiotic is needed for the MDRO target pathogen.
- The risk estimate prompt functions accurately for both Emergency Department and hospital-based physicians.

How the indications screens work

Physicians are required by national regulation to indicate why an inpatient antibiotic is prescribed. When a physician in either Arm 1 or Arm 2 orders an antibiotic for an abdominal (ABD) infection, this indication will be captured and recorded so that the frequency of antibiotics tied to ABD indications can be compared across the arms. One complexity is that physicians can pick “sepsis” which is a non-specific indication.

Because sepsis can be due to an ABD infection, these indication screens will be modified for the trial to have a secondary prompt If sepsis is selected. This additional screen will ask if the sepsis is from an ABD source. If 'yes,' the ABD infection risk estimate and prompt functionality will be triggered in intervention facilities.

How the CPOE prompt screens work

Based on the indication screens, if an extended-spectrum antibiotic (Table 1) is ordered and the indication is ABD infection, the CPOE system will acquire the patient and hospital characteristics that best discriminate whether the risk of an antibiotic-resistant infection is above or below 10%.

Table 1: Extended-Spectrum Antibiotics and Associated Pathogen Addressed in the Computerized Physician Order Entry (CPOE) Alert

Antibiotic Ordered	Pathogen Included in Risk Estimate
	Abdominal Infection
Daptomycin	MRSA, *Enterococcus*
Linezolid[1]	
Vancomycin (IV only)	
Ceftaroline	
Aztreonam	*Pseudomonas*
Cefepime	
Ceftazidime	
Piperacillin/Tazobactam	
Ertapenem	ESBL, GNR Resistant to cephalosporins and penicillins
Imipenem	ESBL, GNR+*Pseudomonas* Resistant to cephalosporins and penicillins
Meropenem	
Ceftolozane/Tazobactam	

1. Both oral and intravenous formulations of drugs in this category are included.

2. For anti-CRE medications, all models show <10% patient risk for having a highly drug resistant pathogen warranting the use of these drugs. Therefore, patient specific risk estimate will not be calculated and a static CPOE screen will be developed that will recommend avoiding empiric use without consultation with antibiotic stewardship team or infectious diseases.

3. Newly released ES medications require ID approval and will be considered for inclusion in the CPOE prompts on a case by case basis

Abbreviations:

MRSA - Methicillin Resistant *Staphylococcus aureus*

GNR – Gram Negative Rod

ESBL – Extended-Spectrum Beta Lactamase producers

MDR- Multidrug-resistant

4. Antibiotics list subject to change as newly licensed antibiotics will be added as needed

The precision-medicine risk calculation will be provided in real-time to physicians when they order an antibiotic in the CPOE system. If the risk is ≥10%, the provider will be able to finalize the order without any prompt. If the risk is <10%, the provider will receive a prompt stating that the "[specific extended-spectrum antibiotic] is not recommended because the patient's risk of [the relevant antibiotic resistant pathogen] is <10%." The prompt will then recommend a standard spectrum antibiotic and ask the provider if they would like to accept the replacement (one-click solution) or override the suggestion by entering a reason.

The Cancel button returns the clinician to the previous order screen and the Replace button will launch an order screen for the recommended standard-spectrum antibiotic. Clinicians choosing to override are asked to indicate the reason in a subsequent screen.

CPOE Personalized Risk Estimate Prompt Data Capture

When a clinician places an antibiotic order for a patient with ABD infection due to an MDRO, the CPOE personalized risk estimate prompt screen will use the patient's specific Electronic Health Record (EHR) data to calculate the MDRO risk based on previously developed models from over 422,000 HCA Healthcare patients with ABD infections within the HCA Healthcare Clinical Data Warehouse (CDW). As described above, if the risk is low (<10%), the risk estimate prompt will recommend a standard-spectrum antibiotic. If the risk is ≥10%,

the risk estimate prompt will allow the clinician to proceed with the ES order, without any additional prompts. At the time of the order, if the patient is in the ED, the first prompt will ask if the patient is ICU-bound. If the patient is ICU-bound, the risk estimate prompt will not fire when the clinician proceeds with ordering an antibiotic.

The MDRO risk estimate models that feed in to the CPOE personalized risk estimate prompts will be developed using hundreds of thousands of patients within the HCA Healthcare CDW, using 3 years of data. Several MDRO risk factors will be evaluated including:

- Each HCA Healthcare hospital's local antibiogram for ABD infection patients
- Risk factors for MDRO infection
  - Demographics
  - Comorbidities
  - MDRO or *Pseudomonas* history
  - Recent admission, ED visit, nursing home care
  - Recent antibiotic use

Labs

Statistical analysis will then be performed on the above variables to identify which variables are most often found in patients who develop ABD infection with an MDRO. Using these risk factors (which differ for every MDRO), the CPOE risk estimate prompt gives the patient's absolute risk for infection with the MDRO(s) targeted by the antibiotic ordered.

Trial Toolkit

Site study champions will receive an arm-specific trial toolkit (see Table 2 below) with protocols and educational materials, including frequently asked questions (FAQs) for providers and pharmacists. Additional FAQs will be added during the trial, as needed.

Table 2. Contents of INSPIRE-ASP Trial Toolkit Binders

Educational Material	Description
1. Welcome and Summary of Goals	Introductory information on the trial
2. Study Investigators	Lists all investigators and collaborators involved in the trial
3. Table of Contents	Summary of documents included
4. Phone Matrix	Contact information for lead investigators, HCA Healthcare co-investigators, and study staff
5. Roles & Responsibilities	Describes expectations of hospital study champions
6. Antibiotic Selection Protocol	Protocol for clinicians and prescribers providing overview of antibiotic select that occurs when INSPIRE-ASP CPOE alerts are activated
7. Study Champion Materials	Study Champion trial launch checklist, Frequently Asked Questions (FAQs)
8. Clinician Education Materials	FAQs, Do's and Don'ts, education presentation providing overview of trial, CPOE prompt background and development, CPOE prompt monitoring and feedback
9. CPOE Clinician Workflow	Visual guides for antibiotic ordering with the CPOE smart prompt screens
10. Clinician Progress Report Example	Describes process for monitoring CPOE prompt usage by clinician prescribers; includes sample tables and graphs to be used by study champions to feed back to clinicians

E.2.2 Intervention Phase Activities

During the intervention phase, monthly coaching calls and regular check-in conference calls between each Arm 2 facility and the study team will continue. The CPOE risk estimate will fire for the duration of the trial and the toolkit will continue to be updated with FAQs as needed.

Tableau Clinician Auditing and Feedback Report

A feedback report will be developed by HCA Healthcare corporate IT, using Tableau, an electronic based platform that has been used in several of our previous HCA Healthcare multi-center trials. The feedback report will provide facility level data on acceptance of the CPOE risk estimate prompt empiric antibiotic recommendations and evaluate broadly, "at-a-glance," what acceptance rates are among clinicians at the site.

The intent of the report is for local Study champions to feed back to local clinicians on acceptance of the CPOE risk estimate prompt empiric antibiotic recommendations. Study Champions will be educated via webinars on how to use the Tableau dashboard, interpret the data, and compile reports to feed back to prescribing clinicians. Summaries can be viewed at the facility and clinician level ES antibiotic selection by indication. Several filtering options will be available on the Tableau Report for Study Champions or other local users to compare and track clinician acceptance or non-acceptance of the CPOE risk estimate prompt recommendations.

Several filtering options will be available on the Tableau Report for Study Champions or other local users to compare and track clinician acceptance or non-acceptance of the CPOE risk estimate prompt recommendations:

- **Acceptance and Non-Acceptance Summary Reports** - Study Champion can use this filter to look at overall acceptance or non-acceptance of empiric antibiotic recommendations.
  - This summary level report will be available as an initial view of overall acceptance or non-acceptance for (1) clinician-level and (2) hospital-level acceptance (compared to other Arm 2 facilities). It will allow for range filtering for viewing data across designated periods of time that allows trending.
  - This option will be available for viewing/printing summary tables and graphs with de-identified clinician information.
  - This report will be able to be filtered by initial antibiotic ordered.

- **Antibiotic Prescribing Per Protocol** - defined as # (%) of per-protocol antibiotic prescribing among patients with ABD Infections. This gives clinicians credit for choosing standard spectrum antibiotics that never required a trigger in the risk estimate prompt.

- **Emergency Department (ED) ICU-Bound Prompt Report** - INSPIRE CPOE workflow includes a prompt to ED clinicians asking if the patient is ICU-bound. If response is "yes" then no further CPOE screens will fire. This report allows study champions to see how often ED clinicians respond "yes" to assess whether clinicians may be circumventing the prompt.

- **Prompt Report** - This report provides the # or % of opportunities that results in a CPOE risk estimate prompt activation.
  - Allows filtering by prompt action chosen (cancel, override, replace)

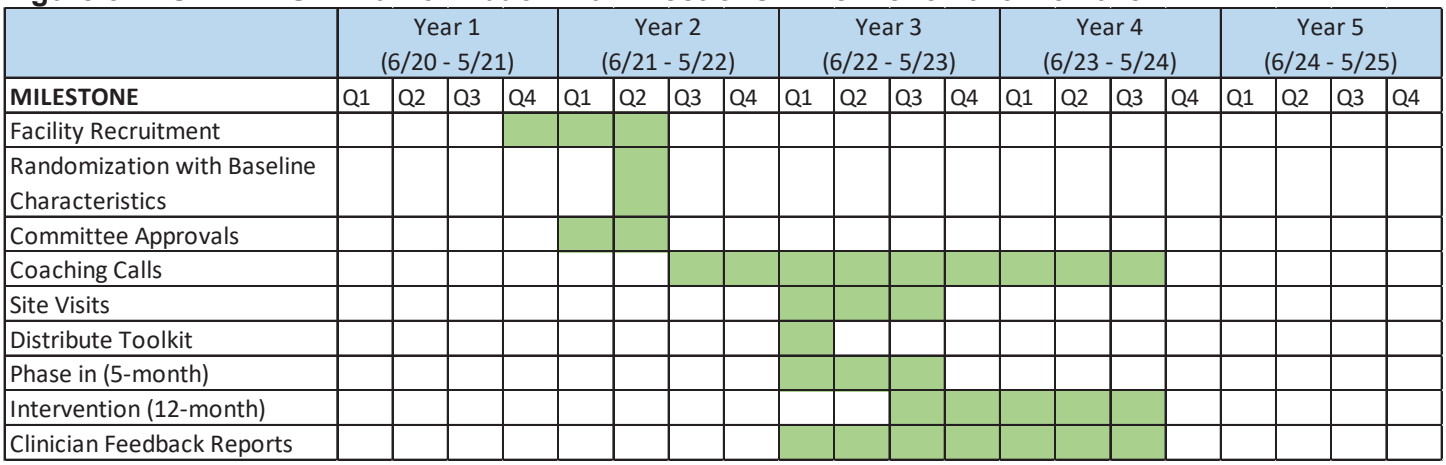
- **Override Report** – Some pharmacists may want to be able to filter by type of override for intended follow up plan that day. They may know they are going to round in the ICU, they may want to print out a list of all overrides due to ICU-bound and check to see if they actually went to the ICU while they were there, or they may be doing medication reconciliation with allergies and want a printout of all the overrides due to allergies and cross check those simultaneously.

- **Extended-Spectrum (ES) Indications Report** – For use if Study champion would like to organize by ES antibiotic orders and by indication.

F. Study Schedule

The timeline for the trial is shown in Figure 3 below, with key milestones indicated.

Figure 3. INSPIRE-ASP Trial for Abdominal Infections Timeline: 6/2020 – 5/2025



G. Assessment of Outcome Measures

G.1. Data Sources and Collection

Trial data will not be collected by participating sites. Instead, all variables and outcomes will be obtained from custom extractions from the HCA Healthcare computerized data warehouse. HCA Healthcare has a long-established corporate data warehouse with admission data, demographics, diagnostic and procedure codes, CPOE data, and laboratory and pharmacy data. Trial data from the computerized data warehouse will include demographic, insurer, comorbidity, and laboratory (including microbiology) data for ABD infection cohorts.

G.2. Specifications of the Appropriate Outcome Measures

The primary, secondary and safety trial outcomes are summarized below in Table 3.

G.3. Primary Outcome Measures

The primary trial outcome for ABD infections reflects the national metric of days of therapy (DOT) of extended-spectrum antibiotic use (ES-DOT), which we will evaluate for the empiric period (hospital day 1-3). Trial success will be based upon the relative reduction in this metric between the INSPIRE Stewardship Bundle vs routine care arm when accounting for baseline values.

G.4. Secondary Outcome Measures

There will be two secondary outcomes for ABD infection (antipseudomonal DOT and vancomycin DOT).

G.5. Safety Outcomes

Two safety outcomes will also be assessed. We will evaluate if increased use of standard-spectrum antibiotics causes increased ICU transfers or hospital length-of-stay.

Table 3. Trial Outcomes

Outcome	Metric for ABD Cohort
Primary Trial Outcome: Total Empiric Extended-Spectrum Antibiotic Days of Therapy (ES-DOT)	The number of different extended-spectrum antibiotics each empiric day, summed across the first 3 days of hospitalization.[1]
Secondary Trial Outcomes: Vancomycin Days of Therapy across Empiric Day and Total Empiric Antipseudomonal Antibiotic Days of	The number of days Vancomycin was received on the first 3 days of hospitalization.[1]
	The number of different antipseudomonal antibiotics each empiric day, summed

Therapy (ES-DOT)	across the first 3 days of hospitalization.[1,2]
Safety Outcomes: ICU Transfer and Length-of-Stay	Intensive Care Unit (ICU) Transfer: Days to ICU transfer, from hospital days ≥ 3 and ≤ 14
	Length-of-stay: Days from hospital admission until discharge or hospital day 14, whichever comes first, where admission day is hospital day 1.

[1]E.g., if a patient is admitted for 2 days, ES-DOT will be calculated across those 2 days; however if a patient is admitted for 4 days, only the first 3 days will be evaluated.
[2]Does not include aminoglycosides or fluoroquinolones

H. Statistical Considerations

H.1. Criteria for Discontinuation or Withdrawal

As a pragmatic trial of a quality improvement protocol, follow-up of the analytic cohort will be assured. It will involve the entire hospitalization as recorded in the electronic health record. Drop-outs will not be applicable at the patient level.

Hospitals can withdraw participation at any time. New antibiotic stewardship interventions affecting prescriptions in the empiric period or changes in EMR system that affect antibiotic order entry (e.g., Patient Keeper, Meditech Expanse) will be assessed by the steering committee for possible conflict and withdrawal of participation (for as treated analyses) during the trial. All participating facilities (via the Study Champion) will report any new proposed initiatives via the study email or in response to a standing polling question on every coaching call. Sites will be trained to understand why competing interventions could jeopardize the findings of the study. Should the Steering Committee identify a conflict, we may report back to the Study Champion to request the facility delay implementation of the new initiative until the trial has ended. If the facility is unable delay implementation, we will conduct an analysis at the end of the trial to assess the impact of interventions on the trial outcomes, or if the impact to the trial is significant, the facility may be asked to drop from the trial (for as treated analysis).

H.2. Study Outcome Measures

See Section G. above.

H.3. Analysis Plan

Primary Statistical Analysis

The primary trial outcome is defined as the summed number of different ES antibiotics received during each empiric day. An empiric day is a day within the first three days of an admission. We define this outcome as the Total Empiric Extended-Spectrum Days of Therapy (ES-DOT). For clarity, the calculation is as follows: we define a DOT for a particular ES antibiotic as a day in which any number of doses of that antibiotic is given. Different ES antibiotics are summed within each empiric day for each patient admission to determine DOT in that at-risk day. Antibiotics given during an associated emergency department visit on the date of hospital admission are counted toward the ES-DOT of the first hospital day.

The main trial results will be based upon as-randomized, unadjusted analyses of admission-level ES-DOT. In contrast to the national DOT measure defined by CDC for hospitals, we define ES-DOT at the individual admission level so that we can perform analyses on individuals.

The trial will be assessed among the cohort of adult admissions who: 1) have administrative claims codes indicating an abdominal infection is present on admission; 2) received any antibiotic within 3 days of admission; and 3) were admitted to a non-ICU location. For admissions initially on a non-ICU floor and transferred to the ICU, analysis will include only admission days on the non-ICU floor within 3 days of admission.

The trial periods are defined as follows: (1) Baseline: January 1, 2019 – December 31, 2019 (12 months); (2) Phase-in: August 2, 2022 – December 31, 2022 (5 months, does not contribute to analysis); (3) Intervention: January 1, 2023 – December 30, 2023 (12 months). The main evaluation of all outcomes will be difference-in-difference between the Intervention and Baseline periods and between study arm. Trial analysis will use a baseline period prior to the arrival of the COVID-19 pandemic since hospital operations and case mix were severely impacted by this pandemic between Winter 2020-Spring, 2022.[25-29] Although at the time of this

writing (June, 2022), COVID-19 surges continue to occur nationally, clinical operations and patient case mix at most hospitals have largely returned to near pre-pandemic activity in the setting of widespread vaccination and milder virus strains. Phase-In is scheduled for August, 2022 as participating hospitals are in a state of recovery sufficient to launch the trial intervention with pharmacy/physician engagement.

The unit of analysis will be individual admissions. Individuals can contribute more than one admission. The analytic model will be a generalized linear mixed effects model for differences in differences, with random effects accounting for correlation within cluster, period-varying random effects to allow for differences within hospitals between baseline and follow-up, and admission-level random effects to account for correlation within person and hospital, if sufficient data exist. We plan to use a Poisson model for analysis of outcomes as follows:

$$log(y_{ijph}) = \beta_0 + \beta_1 A_{ijph} + \beta_2 T_{ijph} + \beta_3 A_{ijph} T_{ijph} + b_{0h} + b_{1h} T_{ijph} + g_j + \log\,(ed_j)$$

where y_{ijph} is the ES-DOT for patient i for admission j in period p at hospital h, and $A_{ijph} = 1$ if hospital h is in the intervention arm and 0 if not, and $T_{ijph} = 1$ if p is the intervention period and 0 if baseline period. The random effects b_{0h} and b_{1h} allow for different baseline mean admission-level ES-DOT for each hospital and each hospital in the intervention period, respectively. Equivalently, they allow for correlation within hospital at different levels at baseline and at follow-up. The random effect g_j allows each patient to have a different mean ES-DOT. Finally, ed_j is the number of empiric days in the admission.

The assessment of trial success will be determined by the significance of the arm by period interaction term β_3, which assesses whether the log relative rate of the outcome due to being in the intervention arm in the intervention period is different from 0. The exponentiated parameter estimate for β_3 is the estimated relative rate of ES-DOT per at-risk day due to the intervention, relative to the baseline period. For example, if β_3 had a negative value and a p-value <0.05, we would conclude that the patient-specific CPOE smart prompts generated a benefit over routine care. Exponentiating the parameter value would provide an estimate of the relative reduction due to the intervention in the expected ES-DOT per at-risk day.

The primary trial analysis will use an as-randomized unadjusted model with two-tailed significance set at alpha = 0.05. Secondary outcomes will be assessed using an as-randomized unadjusted model and will include adjustment for multiple comparisons with two-tailed significance set at alpha = 0.025 for the two secondary outcomes.

Subsequent analyses of the primary and secondary outcomes will include both as-treated and adjusted models. Adjusted models will account for individual characteristics such as age, gender, comorbidities, and prior history of MDROs as well as hospital characteristics such as hospital antibiotic resistance. We will also account for seasonality. All adjusters will be determined a priori. These analyses will be reported as point estimates with confidence intervals and without p-values. The reason for including these analyses is to provide additional information related to the trial outcomes for readers to assess the effects of potential confounders. The reason to not include them in a formal multiple comparisons adjustment is because these analyses are non-independent evaluations relative to the as-randomized unadjusted analyses.

We will separately evaluate intervention period effects by arm alone.

Safety Outcomes

Safety outcomes noted in the above table will be assessed in the most conservative manner to identify potential safety issues. Safety outcomes are required because a reduction in ES-DOT might be achieved only by incorrectly withholding ES antibiotics when they were really needed. Each safety outcome will be evaluated for non-inferiority using an as-randomized unadjusted analysis with a one-tailed significance set at alpha = 0.05. Length-of-stay and days to ICU transfer are evaluated within 14 days of admission since empiric antibiotic selection within the first 3 hospital days is not expected to be a main driver of either outcome beyond this time period; evaluation of baseline data also shows that 93% of abdominal patients have length-of-stay equal to or less than 14 days. Analyses planned for these assessments are proportional hazards models with random effects for each hospital and admission. These models are sometimes called frailty or shared frailty models. Because these are safety outcomes, we do not intend to make adjustments for multiple comparisons in testing them, further increasing conservatism.

All analyses will be performed using current versions of SAS (Version 9.4, as of writing, SAS Institute, Cary NC) and/or R (Version 4.0, as of writing).

C.2.11 Power Size/Sample Size Calculations

Power assessment proceeded as follows, using a Monte Carlo approach.[25] We used available data to define a baseline period of 1/1/2019-12/31/2019. In a bootstrap procedure, individuals were selected with replacement from within each hospital, once to represent baseline data and separately to represent "intervention period" data. Hospitals were then "randomized" to intervention or control according to multiple parameters, including number of admissions with abdominal infection and ES-DOT. We then modified the outcomes for the bootstrapped individuals in the "intervention" period in the "intervention" arm to reflect the effect of the intervention.[29]

We assessed power to identify an overall 12.5% relative reduction in ES-DOT. This effect was implemented by reducing the relative empiric days of therapy for each admission which was exposed to the CPOE prompt. The amount of reduction was a uniform random variate between 0.75 and 1. For example, if the bootstrapped patient initially received 8 ES-DOT and was assigned to have a have a 12.5% reduction, then that admission intervention ES-DOT would be reduced to 7 days (8*0.875=7). The reduction of ES-DOT was selected with a lower bound determined by the investigators as the minimal effect achieved that would be clinically meaningful. Using this method, we have ≥99.9% (99.6-99.9%) power to detect this effect.

Since adoption of the intervention will be heavily influenced by the ability to demonstrate safety, our study size was based on the power to detect non-inferiority for safety outcomes. We used methods similar to the above to calculate the power to identify at least a one day increase in length-of-stay for 12.5% of patients who had hospitalizations less than 14 days and found the power was 91.5% (CI 89.6-93.2%), where non-inferiority is defined as a hazard ratio no smaller than 0.98. For days to ICU transfer, we estimated the power to detect a 2% increase in transfers to the ICU on hospital day 3 through 14 to be >99.9% (CI 99.6-99.9%), where non-inferiority is defined as having a hazard ratio no greater than 1.1 (fewer days to ICU results in a hazard ratio above 1).

For completeness, we note that there are other pre-specified outcomes intended for exploratory analysis in secondary papers for the INSPIRE ABD trial in Table 4 below.

Table 4: Secondary Manuscripts - Other Pre-Specified Outcomes

Secondary Manuscripts (other pre-specified secondary exploratory analyses for later manuscripts)	
Inpatient Extended-Spectrum Days of Therapy after the Empiric Period	The number of different ES antibiotics received each day, on hospital days ≥4 and ≤14.
Empiric and Total Antibiotic Costs	Empiric and total antibiotic costs during hospitalization
Incidence of Hospital-Onset *C. difficile*	Hospital-onset *C. difficile* positive tests (specimen obtained) on hospital days ≥4 and ≤14.
Incidence of Hospital-Onset MDRO-positive Cultures	Newly-detected hospital-onset MDRO-positive cultures on hospital days ≥4 and ≤14. Includes total MDRO and specific MDRO subsets.

I. Access to Source Data/Documents

To protect the large volume of protected health information required for the INSPIRE-ASP Abdominal Infections Trial, HCA Healthcare will establish a mechanism similar to our previous trials where the study's programmer analysts gain access to HCA Healthcare data behind the HCA Healthcare firewall. Programmer analysts will receive remote access to an HCA Healthcare web server where requested data will be placed after extraction by HCA Healthcare information technologists. This extraction process will involve replacement of names and medical record numbers with coded identifiers. Programmers will access this virtual machine to clean and analyze data, and to generate summary level output for review with our statistician.

J. Quality Control and Quality Assurance

Monthly data will be accessed by study data analysts from the HCA Healthcare CDW behind their corporate firewall. We anticipate extracting data monthly to be able to validate the data streams. Data stream validation involves initial validation by HCA Healthcare to ensure the integrity of data capture and transfer from individual hospital electronic data systems to the HCA Healthcare corporate centralized data warehouse. This will occur under general HCA Healthcare operations and has a <<1% error rate.

The study programmer analysts will assess each data element for variation within and across hospitals within individual streams. Data cleaning will involve assessing missing data and unusual month-to-month variation in data elements. Data discrepancies will be resolved by revised data extraction methods, particularly those requiring multiple data streams, and by performing quality control checks on the programming code.

K. Subject Confidentiality

K.1. Future Use of Stored Specimens

This study will not include any stored specimens.

K.2. Subject Confidentiality

To protect the large volume of protected health information required for the INSPIRE-ASP Abdominal (ABD)Infections Trial, study programmer analysts will gain access to HCA Healthcare data behind the HCA Healthcare firewall. Programmer analysts will receive remote access to an HCA Healthcare web server where requested data will be placed after extraction by HCA Healthcare information technologists. This extraction process will involve replacement of names and medical record numbers with coded identifiers. Programmers will access this virtual machine to clean and analyze data, and to generate summary level output for review with the study's statistician.

L. Ethics /Protection of Human Subjects

L.1. Centralized Institutional Review Board (IRB) Process and Prior Experience

As a pragmatic cluster-randomized trial of an antibiotic stewardship quality improvement strategy, we will request a minimal risk determination consistent with our prior HCA Healthcare clinical trials. Reasons supporting a minimum risk determination are: 1) the protocol is guideline-concordant, 2) prompts provide risk estimates and recommendations, but does not supplant clinical judgment, 3) evidence suggests that there is time to wait for culture results in non-ICU patients instead of using empiric extended-spectrum antibiotics for uncommon resistant organisms.

Similar to all prior HCA Healthcare clinical trials, the Harvard Pilgrim Health Care (HPHC) IRB will approve a centralized IRB protocol and coordinate reliance agreements with participating hospitals with support from HCA Healthcare's corporate regulatory affairs liaison (David Vulcano MBA, Vice President, Research Compliance and Integrity). In prior trials, IRB approval can be obtained within 2-3 months and the reliance process can occur in a rolling fashion during recruitment, overall requiring an additional 3-4 months.

L.2 Informed Consent Process

Similar to our prior pragmatic trials, we expect that this intervention of a quality improvement strategy for antibiotic stewardship will meet national regulatory standards for waiver of informed consent under the Office of Human Research Protections (OHRP) criteria 45 CFR 46.116(d), 117(c) since 1) trial activities meet minimal risk criteria, 2) the trial randomizes hospitals, not patients, to a quality improvement strategy, 3) the intervention is not designed to supplant physician judgment, but rather provide relevant information to prescribing physicians who will be educated to choose the treatment they deem most clinically appropriate for individual patients, and 4) all assigned activities will be performed according to usual hospital quality improvement procedures outlined by hospital antibiotic stewardship programs. We will also collect attestations from hospital antibiotic stewardship programs stating that they will continue routine antibiotic stewardship efforts.

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