NIH Collaboratory Ethics and Regulatory Core: Consultation Call
Intelligent Stewardship Prompts to Improve Real-Time Empiric Antibiotic Selection for Patients (INSPIRE)
January 30, 2023; 2:00-3:00 pm ET (via Zoom)

Participants:

- Core and Coordinating Center: Joe Ali (Johns Hopkins University), Carole Federico (Stanford University), Kate Jaffe (University of Michigan), David Magnus (Stanford University), Stephanie Morain (Johns Hopkins University), Pearl O'Rourke (retired), Vasiliki Rahimzadeh (Stanford University), Tammy Reece (Duke University), Damon Seils (Duke University), Kayte Spector-Bagdady (University of Michigan), Kevin Weinfurt (Duke University), Benjamin Wilfond (University of Washington)
- Demonstration Project team: Shruti Gohil (University of California, Irvine), Clayton Huntley (NIAID), Laurie Kunches (Harvard Pilgrim Health Care), Richard Platt (Harvard Pilgrim Health Care), Paula Tebeau (Harvard Pilgrim Health Care)
- NIH: Robin Boineau (NCCIH), Beda Jean-Francois (NCCIH), Kevin McBryde (NCCIH), Wendy Weber (NCCIH)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
Overview of Demonstration Project	NIH Pragmatic Trials Collaboratory Demonstration Project teams typically engage in a consultation with the Ethics and Regulatory Core at the beginning of their UG3 planning phase, then revisit the issues discussed in that consultation during a follow-up consultation after their transition to the UH3 implementation phase. The INSPIRE Demonstration Project joined the NIH Collaboratory after its planning phase was complete and its UH3 implementation phase was beginning. Meeting attendees received the Research Strategy and IRB protocols for the INSPIRE Demonstration Project prior the meeting. Core members, INSPIRE team members, NIH Pragmatic Trials Collaboratory Coordinating Center staff, and guests introduced themselves. The INSPIRE team members present included Shruti Gohil and Richard Platt. **Project overview**: Lead investigator Shruti Gohil gave a brief overview of the project. INSPIRE is studying the effectiveness of a personalized clinical decision support	

These minutes were circulated to all participants in the call for 1 round of review and reflect all corrections that were received. The project's Abstract and Specific Aims are included as supplementary material.

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	program in improving antibiotic prescribing for non–critically ill patients hospitalized with abdominal infections or skin and soft tissue infections. The trial is comparing routine care under hospital-based antibiotic stewardship programs with an enhanced program that adds a predictive algorithm to promote guideline-concordant prescribing of extended-spectrum antibiotics. In the intervention group, the computerized provider order entry system at sites prompts physicians when extended-spectrum antibiotics are ordered for patients in whom the risk of an antibiotic-resistant organism infection is calculated to be low (less than 10%). The trial promotes guideline-concordant recommendations for antibiotics that are already routinely used in clinical care. It is a "soft stop" prompt that allows the physician to override. The order entry prompt is part of a stewardship bundle that includes education and feedback about individual and group performance. The primary outcome is the use of extended-spectrum antibiotics during the first 3 days after admission. The study timeline is 12 months. The study completed a 5-month phase-in period and recently began full implementation. **Healthcare system partner**: HCA Healthcare **NIH Institute Providing Oversight**: National Institute of Allergy and Infectious Diseases (NIAID) Core members had no questions about the project overview.	
FDA guidance on clinical decision support tools	Before reviewing the standard list of questions for the Core's consultation with new Demonstration Projects, the group discussed the applicability of recent FDA guidance regarding clinical decision support software functions that may be considered to be devices: Clinical Decision Support Software Guidance for Industry and Food and Drug Administration Staff (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-decision-support-software) to INSPIRE. Kevin McBryde of the NCCIH Office of Clinical and Regulatory Affairs shared a graphic that provides a general overview of criteria in the guidance for determining whether a	Core members to send Wendy Weber suggestions of representatives of Demonstration Projects who may have had experience using artificial intelligence or algorithms in clinical decision support to potentially participate in a

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	clinical decision support software function is considered a device subject to additional regulation: Your Clinical Decision Support Software: Is It a Medical Device? (https://www.fda.gov/medical-devices/software-medical-device-samd/your-clinical-decision-support-software-it-medical-device). Laurie Kunches, chair of the IRB that reviewed the INSPIRE protocol, stated that she believed the software being used in INSPIRE clearly fit the non-device category according to FDA criteria 1, 2, and 3. For criterion 3, they believed the alert did not offer a real risk score but simply a yes-no likelihood threshold for informing decision making to use guideline-concordant empiric antibiotics, highlighting the specific non-device example provided by FDA: "clinician guidelines matched to patient-specific medical info." There was additional discussion of criterion 4, but the IRB remained comfortable considering the software to not be a device, because the alert is part of a larger package of clinician education. Joe Ali agreed, noting that the intervention's clinician interface offers a button linking the clinician to more information. Vasiliki Rahimzadeh also agreed with some hesitation because the clinicians are unable to independently verify the "basis for such recommendations" (that is, the antibiotic risk estimate behind the 10% threshold). The investigators noted that extensive efforts were put into place to educate clinicians on how the prompt works and how patient risk estimates are calculated, which will be ongoing throughout the intervention period. This information could not practicably be included in the order entry prompt due to limitations in screen size/programming. Pearl O'Rourke commented that the IRB seems to have conducted a careful and comprehensive review. She agreed with the IRB's determination that the intervention does not qualify as a device, while observing that INSPIRE falls in a gray area with respect to the FDA guidance. She remarked that clarification of how to apply the FDA guidance on this topic would be helpful. The discussion of this study can inform future studies that plan to use clinical decision support software. David Magnus agreed and wondered whether the study would be a useful paradigm example for consideration by the FDA. Clayton Huntley mentioned that, because the FDA guidance is so new, it is	discussion about these issues at the Steering Committee meeting.

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	not clear that NIAID, through its independent monitoring function, would bring any additional experience for the study's IRB to consider. Wendy Weber noted that the FDA is being invited to engage in discussion with a number of investigators for whom this guidance may or may not apply at the upcoming in-person NIH Collaboratory Steering Committee meeting. Reviewing completed Demonstration Projects that have used artificial intelligence or algorithms in clinical decision support as examples would be helpful for that discussion. She asked that Core members send ideas for panelists to include.	
Status of IRB approval	Harvard Pilgrim Health Care is the single IRB of record. The study received IRB approval and is ongoing.	
Risk classification	The IRB determined the study as being no more than minimal risk.	
Consent	A waiver of consent was approved by the IRB. Pearl O'Rourke asked whether the educational materials provided to clinicians as part of the intervention package—including informational posters placed in the clinics—are available to patients in the study. Shruti Gohil responded that the materials are kept in physician work rooms not accessible to patients and that study champions are instructed to use them as educational documents for clinicians only. Pearl O'Rourke asked whether the physicians or the patients are the subjects. The investigators noted during the meeting that hospitals and stewardship teams were the randomized subjects; a more accurate statement is that, although hospitals and their stewardship teams were randomized, the study population consists of patient-subjects with physicians and pharmacists as intermediate participants. The target is the enterprise toward meeting guidelines for patient safety.	
Privacy/HIPAA	Data are kept on an HCA server and are deidentified before being accessed by the study team. The study team sees aggregated data only. Analysts use a VPN to access a protected space on an HCA server and only see deidentified data.	

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	Vasiliki Rahimzadeh asked whether the study team can link unique users to the responses they provide, namely their prompt overrides. It would be interesting to know about the consequences for physicians who override the prompt based on poor rationales, or at least those whose decisions do not cohere with the standard of care. Shruti Gohil responded that the study team is not able to view any clinician progress reports directly, only HCA stewardship teams are able to view those; the study team has access to physician response/actions but is blinded to provider ID numbers and sees only aggregated data.	
Monitoring and oversight	The participating hospitals/stewardship teams will submit regular feedback reports on overrides and replacements. The investigators discussed the need for a DSMB with the trial Steering Committee and with the NIAID science officer (Clayton Huntley) and determined that a data safety monitoring plan would be appropriate in lieu of a DSMB. The data safety monitoring plan was approved by NIAID.	
Issues beyond the study	Clayton Huntley asked what the FDA might say about a system that was already in place when the new guidance on clinical decision support tools was issued. Pearl O'Rourke stated that the documentation of the IRB's review of the matter will carry weight. Kevin McBryde mentioned that the general rule of thumb is that there is discretion in enforcement. If there was no guidance at the time the study began, the FDA takes that into account, and they also would generally be expected to review what was discussed by the IRB and defer to the IRB's determination if there was a thoughtful consideration of the issue.	
Other matters	David Magnus asked about the diversity of the evidence base for both the practice guidelines and the algorithmic model to ensure that it is representative of all patients. Shruti Gohil responded that HCA's patient base and hospital base include a highly diverse population across the nation. With regard to the guidelines, they are broad and do not specify risk subgroups by race/ethnicity.	

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	Pearl O'Rourke asked what will happen with the data and results. Shruti Gohil responded that the primary customers for the results are HCA and the participating hospitals/stewardship teams and that HCA will ultimately decide whether to maintain the prompt and/or disseminate more widely to all of its facilities.	

Abstract

The INSPIRE-ASP Trial (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients) for Abdominal and Skin and Soft Tissue Infections

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 and Skin and Soft Tissue Infections is a cluster-randomized trial to improve judicious antibiotic prescribing for non-critically ill hospitalized patients with abdominal infections or skin and soft tissue infections. Currently, over half of non-critically ill patients with one of these infections receive extended-spectrum antibiotics when less than 5% have an antibiotic-resistant pathogen. The goal of this trial is to advise physicians to prescribe standard- vs extended spectrum empiric antibiotics based on an algorithm that estimates each patient's personalized probability of having an antibiotic-resistant infection. This personalized probability is based upon routinely-collected patient information in the electronic health record and local prevalence of resistant organisms in abdominal or skin and soft tissue infections.

This trial will compare routine care under hospital-based antibiotic stewardship programs to the enhanced program using the predictive algorithm plus audit and feedback to reduce unnecessary empiric prescribing of extended-spectrum antibiotics. In our first aim, we will develop disease-specific prediction algorithms for abdominal infections and for skin and soft tissue infections. In our second aim, this predictive algorithm will be integrated into the computerized provider order entry (CPOE) system to prompt physicians when selected antibiotics are discordant with the estimated need for that antibiotic. Physicians will be prompted to use standard-spectrum antibiotics when the risk of an antibiotic-resistant infection is low. Sixty hospitals will be randomized to either routine care or the CPOE prompt intervention plus feedback. This 18-month study will evaluate ~53,000 patients with abdominal infections and ~37,000 patients with skin and soft tissue infections.

This trial will evaluate the ability of a real-time risk calculator plus audit and feedback to reduce unnecessary extended-spectrum antibiotics while maintaining good clinical outcomes as measured by length-of-stay and transfer to an intensive care unit. These methods will be readily applicable to other electronic health record prescribing systems.

The INSPIRE-ASP Trial (INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients) for Abdominal and Skin and Soft Tissue Infections
Specific Aims

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 and Skin and Soft Tissue Infections is a cluster-randomized trial of 60 hospitals to improve judicious antibiotic prescribing for non-critically ill hospitalized patients. The goal of this trial is to help physicians accurately judge the likelihood that a patient has an antibiotic-resistant infection by using detailed patient characteristics plus local epidemiology so that the best decision can be made for whether standard vs extended-spectrum antibiotics should be used while awaiting culture results.

This trial will evaluate the ability of the real-time risk calculator plus audit and feedback to reduce unnecessary extended-spectrum antibiotics while maintaining good clinical outcomes as measured by length-of-stay and transfer to an intensive care unit. Overall, this trial will determine if a real-time precision medicine risk calculator for resistant pathogens can become best practice for improving judicious antibiotic prescribing in non-critically ill patients.

We will pursue the following Specific Aims:

Specific Aim 1: Develop a real-time precision medicine risk calculator for abdominal (ABD) and skin and soft tissue (SST) infections using patient characteristics and local antibiotic resistance
We hypothesize that personalized risk estimates based upon patient characteristics and local antibiotic resistance data will accurately predict the occurrence of resistant pathogens causing ABD and SST infections.

Specific Aim 2: Conduct a 60 hospital, 90,000 patient cluster-randomized trial comparing routine stewardship to automated personalized prescribing advice to reduce extended spectrum antibiotics in patients with abdominal and skin and soft tissue infections at low risk for antibiotic resistant infection.
We hypothesize that this intervention will significantly reduce days of extended-spectrum antibiotic therapy compared to routine care without adversely impacting clinical outcomes. The intent is to create generalizable knowledge to improve judicious antibiotic use for hundreds of thousands of patients admitted to community hospitals with ABD and SST.