INSPIRE Abdominal & Skin/Soft Tissue Infection Trials

INtelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection for Patients

NIH Collaboratory In-Person Steering Committee Meeting
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INSPIRE Trials Investigative Team Structure

Lead Investigator:	Shruti Gohil, MD MPH, UC Irvine
Senior Investigators:	Susan Huang, MD MPH, UC Irvine Richard Platt, MD MS, Harvard
Analytic Team:	Harvard
Lead Statistician	Ken Kleinman, ScD, U Mass Amherst
Health System Partners	HCA Healthcare: largest private hospital system Jeffrey Guy, MD, HCA Healthcare Kenneth Sands, MD MPH, HCA Healthcare Russell Poland, PhD, HCA Healthcare

INSPIRE Dual Trials: Purpose & Design

- **Purpose:** Reduce unnecessary broad-spectrum antibiotic use in non-ICU inpatients
- **Target Diseases:** 1) Abdominal infection (ABD) and 2) Skin/soft tissue infection (SST)
- **Target Patients:** non-ICU patients in first 3 days of hospital stay
- **Design:** Two cluster-randomized trials
  - Single randomization
  - Two distinct interventions, both received by intervention group
- **Interventions:**
  - Automated disease-specific real-time prompts in MD order entry system that indicates if need for broad-spectrum antibiotics is ≤10% for the prescribing reason of 1) abdominal infection or 2) skin & soft tissue infections
  - Identify admissions with at 10% or greater risk of antibiotic resistance

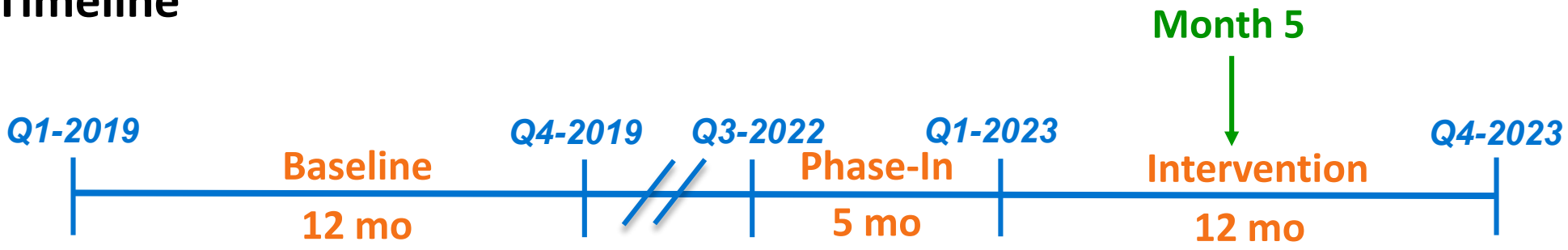
INSPIRE Outcomes

Primary Outcome: Days of any broad-spectrum antibiotic use/eligible days

Secondary Outcomes: Subsets of 1) vancomycin, 2) anti-pseudomonal days/eligible days

Safety Outcomes: 1) days to ICU transfer, 2) hospital length-of-stay

Trial Timeline



Lessons Learned: Accounting for Health System "Over-Recruitment"

- Target recruitment: 60 hospitals out of ~200 → 92 hospitals requested enrollment
- Entire Divisions agreed to participate, health system leadership requests not to limit
- Tradeoff: higher precision versus ethics of over-recruitment
- Recalculated power to assess if could shorten trial from 18 to 12 months

Power sufficient for 12-month trial

	Effect Size	Abdominal Trial Power (CI)	Skin/Soft Tissue Trial Power (CI)
Extended-spectrum days of therapy	12.5% reduction sufficient	≥99.9% (99.6-99.9%)	≥99.9% (99.6-99.9%)
Length of Stay[1]	≥1 day increase for 12.5% of patients	91.5% (CI 89.6-93.2%)	68.9% (CI 65.9-71.8%)
ICU Transfers[2]	2% increase in transfer events	>99.9% (CI 99.6-99.9%)	>99.9% (CI 99.6-99.9%)

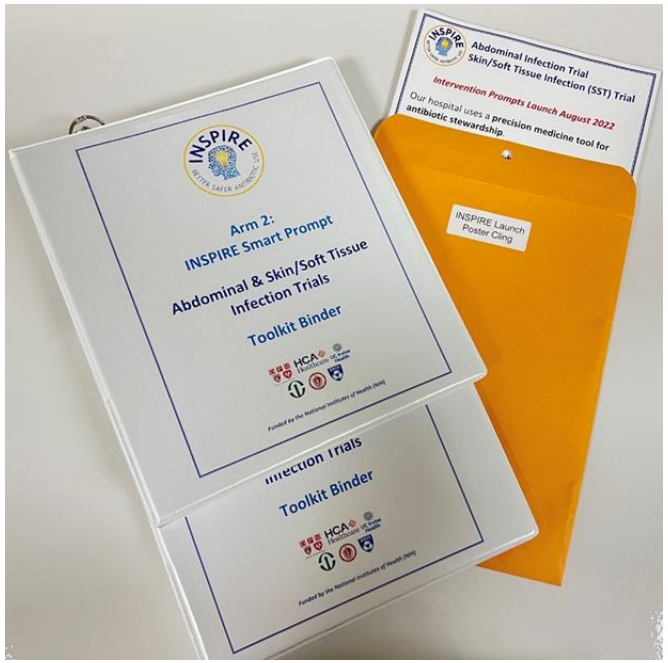
[1]Non-inferiority margin (NIM) defined as hazard ratio no less than 0.98
[2]NIM defined as hazard ratio no higher than 1.1

Implementation: Multimodal Education Rollout

Intervention: Antibiotic Stewardship Bundle (Prompt + Education + Feedback)

- **Coaching Calls**
- **Clinician Education**
  - In-person site visits
  - Handouts, FAQs
  - Presentations
  - Poster clings
  - CMO Emails
  - Podcasts
- **Feedback Reports**
  - Study Champion driven

INSPIRE Study Toolkit



INSPIRE Overview Podcast

Necessity and impact unclear - plan to investigate prior INSPIRE trial rollout by HCA Healthcare without extensive education

Competing Interventions

Strong national pressure to reduce antibiotic use – competing interventions common

- Need to balance between hospital stewardship interests and trial requirements
  - Decision-making done in partnership with HCA Healthcare leadership
- Both study groups are strongly encouraged to continue usual stewardship activities
- Regular outreach to solicit reporting of any potential competing interventions:
  - New antibiotic selection strategy that could impact extended-spectrum antibiotic selection in the first 3 days of hospitalization
- Examples of direct competing interventions
  - Division with multiple Arm 1 and 2 sites reported plans to change order sets that pre-selected INSPIRE's recommended standard-spectrum antibiotics
  - Use of molecular testing for fast turnaround (<2 days) of culture results

Planning Ahead for Quick Turnaround to Publish After Trial Ends

Trial analysis precursor steps currently in process

- Early decisions on manuscript tables/figures while trial is ongoing
  - Discussions with key stakeholders: statistician, health system partners
  - Identify anticipated sub-analyses and structure datasets to accommodate
- Data quality control – monthly reports to identify irregularities
- Cleaning of all data streams with monthly pulls
- Prep and plan coding

Data & Resource Sharing Plan

- Protocols, educational materials will be made public after trial
- Analytic programs developed for evaluation of trial will be made public available
- Data sharing – data exist behind HCA Healthcare firewall and data are owned by health system collaborator
  - We will use a “Supervised Data Enclave” to allow formal request of data and review/release by HCA Healthcare and investigators
- Publication/presentation of results