The INSPIRE Antibiotic Stewardship Trials

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

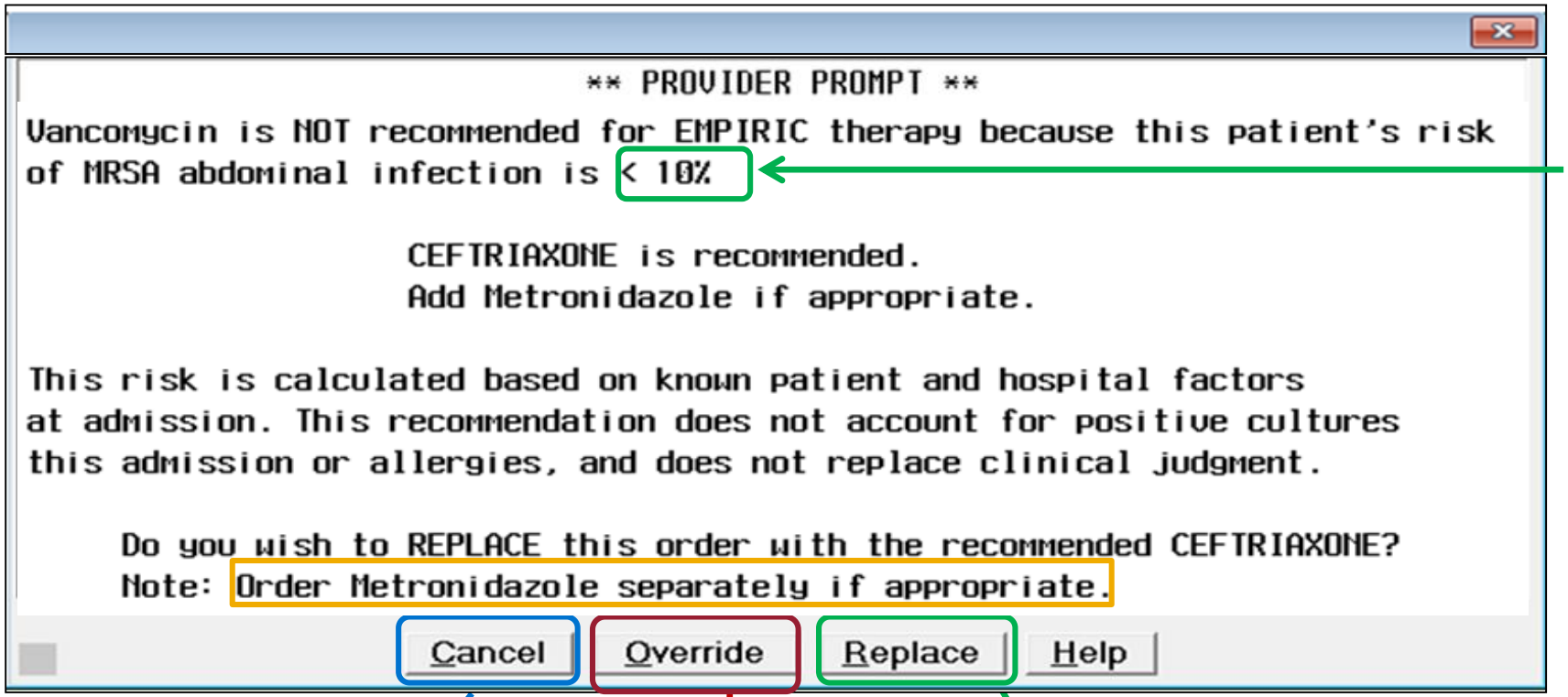
NIH Collaboratory Steering Committee Lightning Rounds

INSPIRE Trials: Purpose & Design

- **Purpose:** Reduce unnecessary empiric extended-spectrum antibiotic use
- **Design:** Cluster-randomized trials, 92 HCA Healthcare hospitals, non-ICU patients
- **Intervention:** CPOE prompts for abdominal or skin/soft tissue infections
- **Outcomes:**
  - **Effectiveness** – antibiotic use first 3 inpatient days
    - Primary – any broad-spectrum antibiotics, secondary – antibiotic subsets
  - **Safety:** days to ICU transfer, hospital length of stay

Intervention: Prompt With Patient-Specific Risk for Antibiotic Resistance

- Physician orders antibiotic, algorithm calculates absolute risk, if risk for antibiotic resistant calculated to be low (<10%), then prompt fires



Absolute risk estimate specific to:

- ✓ Patient
- ✓ Infection
- ✓ Pathogen
- ✓ Hospital

Returns to order screen

Next screen asks reason to keep vancomycin

Taken to ceftriaxone order screen

INSPIRE Abdominal & Skin/Soft Tissue Infection Trials

Results

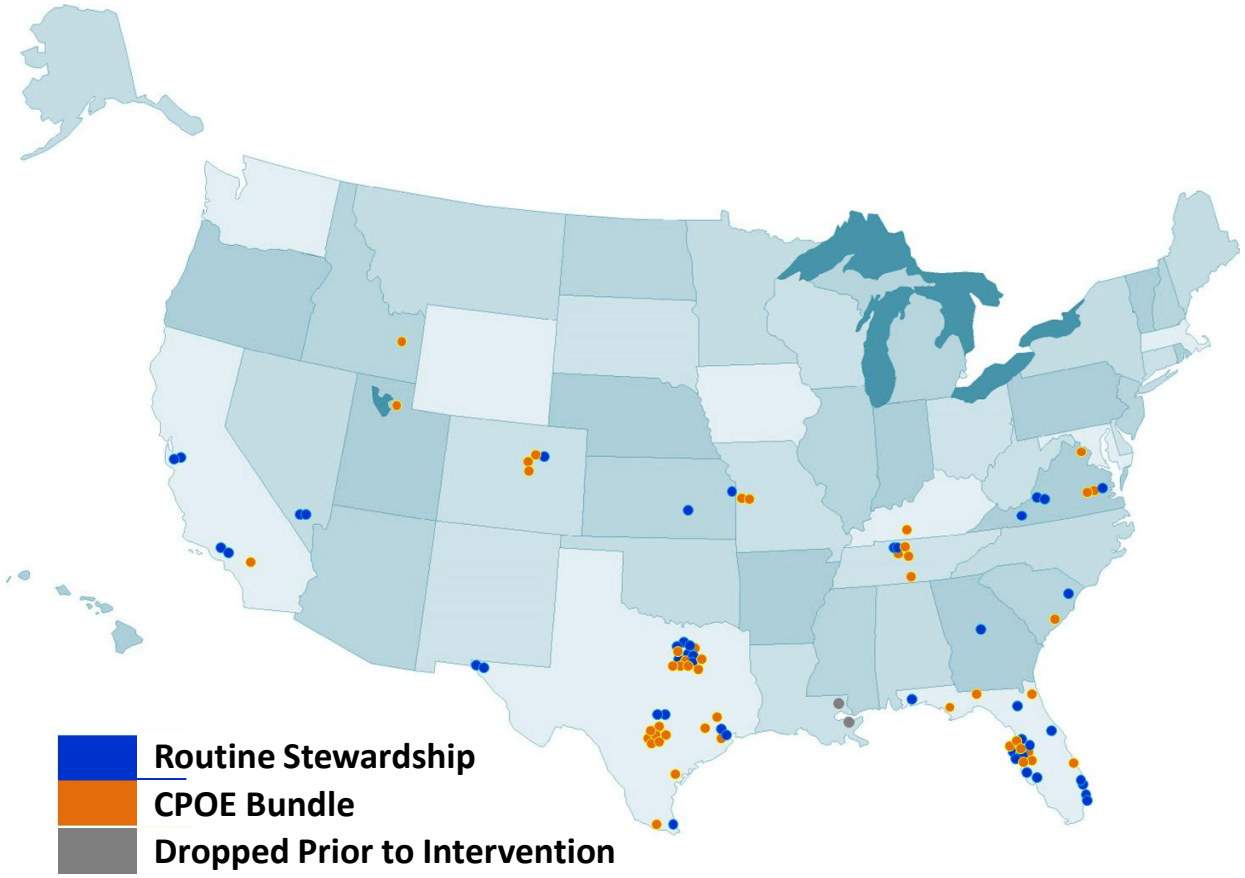
INSPIRE Trial Participants

- 92 hospitals in 15 states
- Non-ICU intervention period admissions – **Abdominal Infection = 105,044**
  Skin & Soft Tissue Infection = 60,725

Routine Stewardship
46 Hospitals
Abdominal Infection Trial: N = 54,384
Skin & Soft Tissue Infection Trial: N = 31,337

CPOE Bundle
46 Hospitals*
Abdominal Infection Trial: N = 50,620
Skin & Soft Tissue Infection Trial: N = 29,388

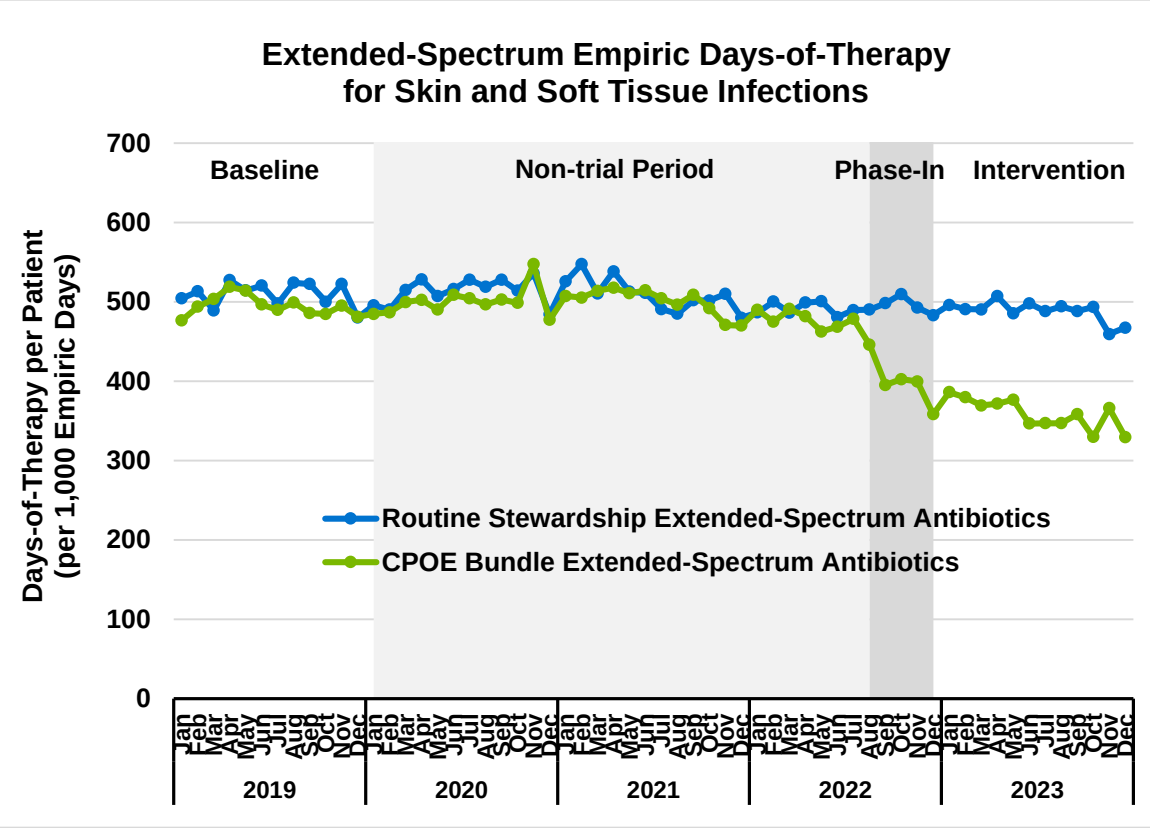
*2 hospitals divested from HCA Healthcare before intervention



Reduction in Empiric Days of Therapy Across Study Period

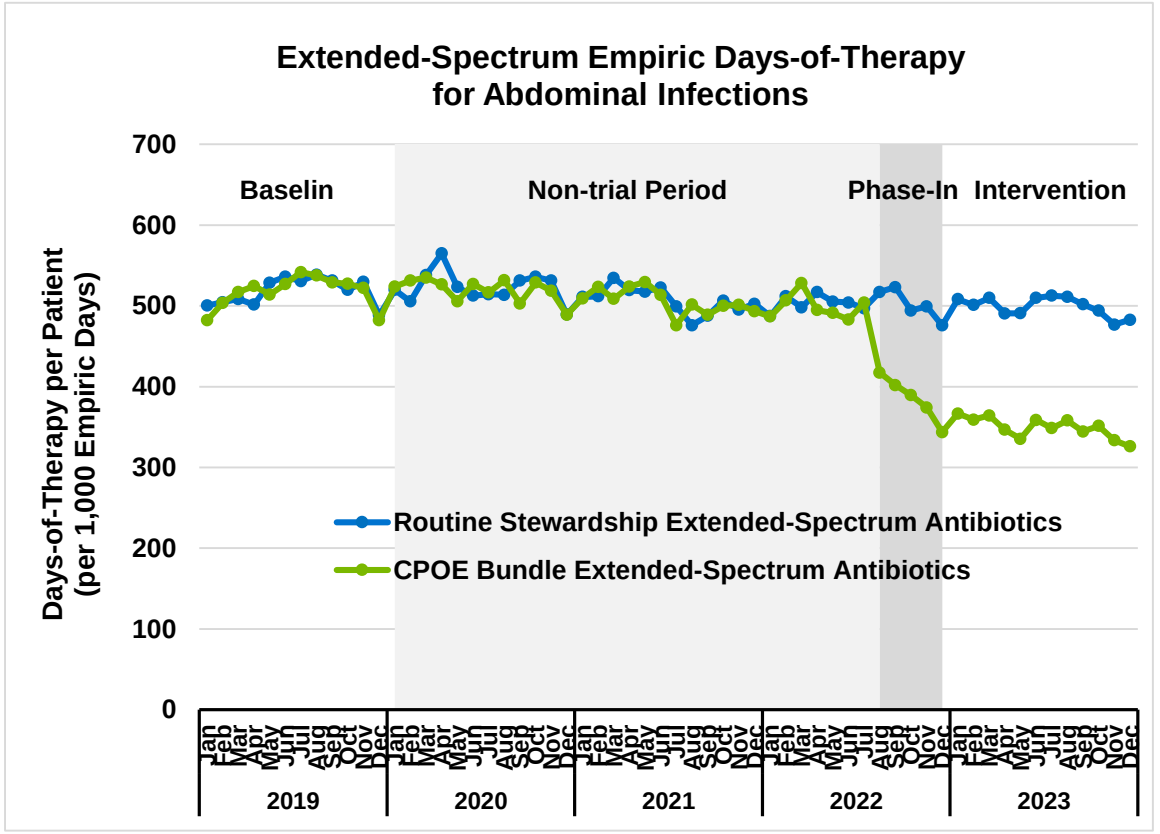
Skin & Soft Tissue Infections

28% crude absolute reduction



Abdominal Infections

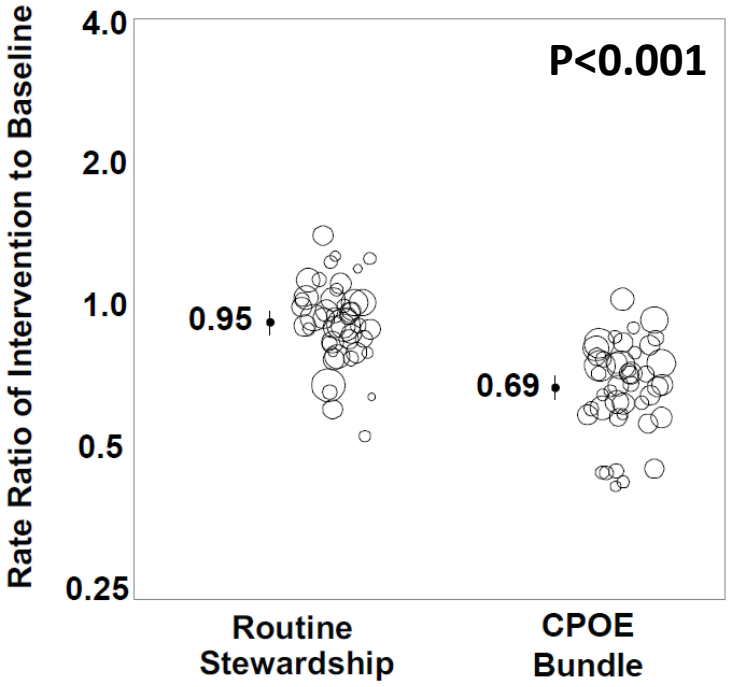
35% crude absolute reduction



INSPIRE Trial Effectiveness Outcomes – As Randomized

Skin & Soft Tissue Infections

Extended-Spectrum Days of Therapy

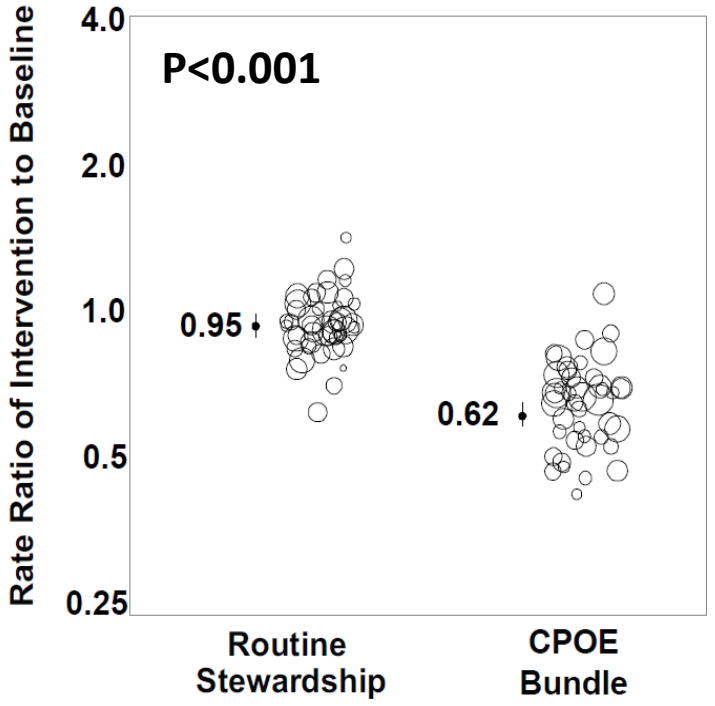


INSPIRE Intervention

28% reduction

Abdominal Infections

Extended-Spectrum Days of Therapy



INSPIRE Intervention

35% reduction

No evidence of inferiority in safety outcomes

INSPIRE Publications & Presentations

2 Trials, >160,000 Patients

- Abdominal infection – ↓35%
- Skin/soft tissue infection – ↓28%

2 Primary manuscripts

1 Editorial

1 Commentary

3 Secondary studies in progress

3 National/international presentations

1 National society research award

Learning Lessons: Robust Randomization Protects Against the Unexpected

- Multivariable randomization
- Weighted 18 different variables
- Very well-balanced study groups

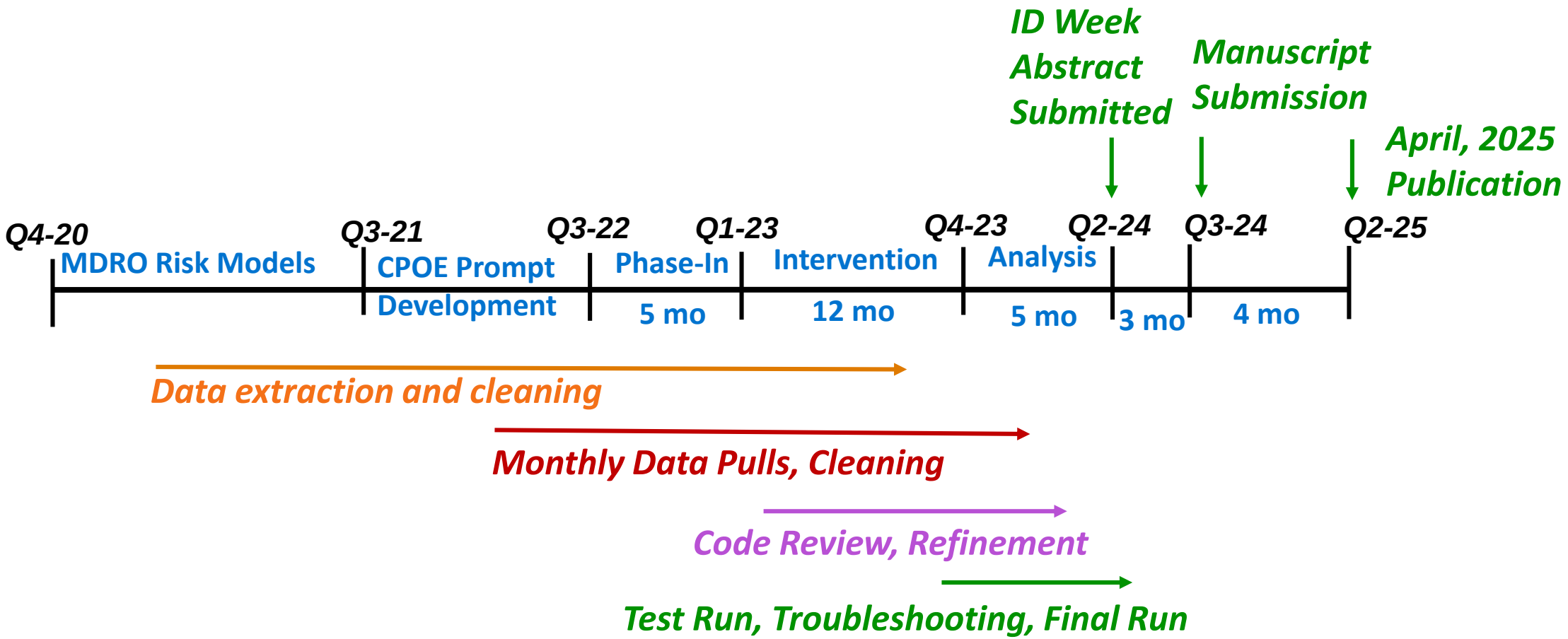
Variable Name
Annual Admissions – Abdominal (ABD)
Annual Admissions – Skin/Soft Tissue (SST)
Extended-Spectrum (ES) DOT ABD
ES-DOT SST
Vancomycin DOT ABD
Vancomycin DOT SST
Antipseudomonal DOT ABD
Antipseudomonal DOT SST
% Admits Cultured - ABD
% Admits Cultured - SST
% SST Admits MRSA positive
Length of stay ABD
Length of stay SST
Mean Elixhauser score ABD
Mean Elixhauser score SST
% ABD Admitted for Surgery
% Admits Meeting >10% Absolute Risk - ABD
% Admits Meeting >10% Absolute Risk - SST

Lessons Learned: Find Shortest Trial Period Needed To Get the Answer

- 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 – what is the shortest intervention period to assess effectiveness but also sufficient to assess safety outcomes?

  → Able to shorten from 18 to 12 months

Learning Lessons: Proactive Steps Can Shorten Time to Trial Analysis



Next Steps

- Secondary manuscripts
- Dissemination
- Follow-up studies

Next Steps: Dissemination

- HCA Healthcare dissemination: activation of prompts to non-trial sites
- Online dissemination toolkit: roadmap for implementation
  - *https://ucihealth.org/healthcare-professionals/inspire*
- Amplify publicity
  - Leveraged media/press teams for joint release through multiple channels
  - Web-based opportunities for feature stories
- Seeking other opportunities to expand adoption
  - Engaging EHR vendors

Next Steps: Future Studies

- Can we improve upon the INSPIRE results?
  - Find and prompt for high-risk patients
  - Change prompt language
  - Assess physician phenotype associated with prompt response
  - Target other infections that are overtreated

PRIM-ER: Primary Palliative Care for Emergency Medicine

May 7, 2024

Memorial Sloan Kettering Cancer Center

Results

- We identified 98,922 initial visits with 51% occurring during the pre-intervention period and 49% in the post-intervention period
- After adjusting for temporal trends and the effects of the COVID-19 pandemic, there was no difference in the primary outcome
- The hospital admission rate was 64.4% during preintervention vs 61.3% during postintervention (absolute difference,−3.1% [95%CI,−3.7%to−2.5%]; adjusted odds ratio [OR], 1.03 [95% CI, 0.93 to 1.14]

Results

Table 1: Sample Characteristics

	Pre-Intervention (N=50458)	Post-Intervention (N=48464)
Age		
Median (Q1-Q3)	77.0 (71.0-85.0)	76.0 (71.0-84.0)
Age in Categories, No. (%)		
66-69	9274 (18.4%)	9904 (20.4%)
70-74	10286 (20.4%)	10436 (21.5%)
75-79	9521 (18.9%)	9490 (19.6%)
80-84	8389 (16.6%)	7674 (15.8%)
85+	12988 (25.7%)	10960 (22.6%)
Sex, No. (%)		
Female	25137 (49.8%)	23904 (49.3%)
Male	25321 (50.2%)	24560 (50.7%)
Race and Ethnicity, No. (%)		
American Indian or Alaska Native	93 (0.2%)	60 (0.1%)
Asian	2042 (4.0%)	1689 (3.5%)
Black	6177 (12.2%)	6863 (14.2%)
Hispanic	2555 (5.1%)	2437 (5.0%)
White	38126 (75.6%)	35891 (74.1%)
Unknown	914 (1.8%)	1018 (2.1%)
Other	551 (1.1%)	506 (1.0%)
COVID Period, No. (%)		
COVID	11795 (23.4%)	43411 (89.6%)
Pre-COVID	38663 (76.6%)	5053 (10.4%)
Gagne Score		
Median (Q1-Q3)	8.00 (7.00-10.0)	8.00 (7.00-10.0)

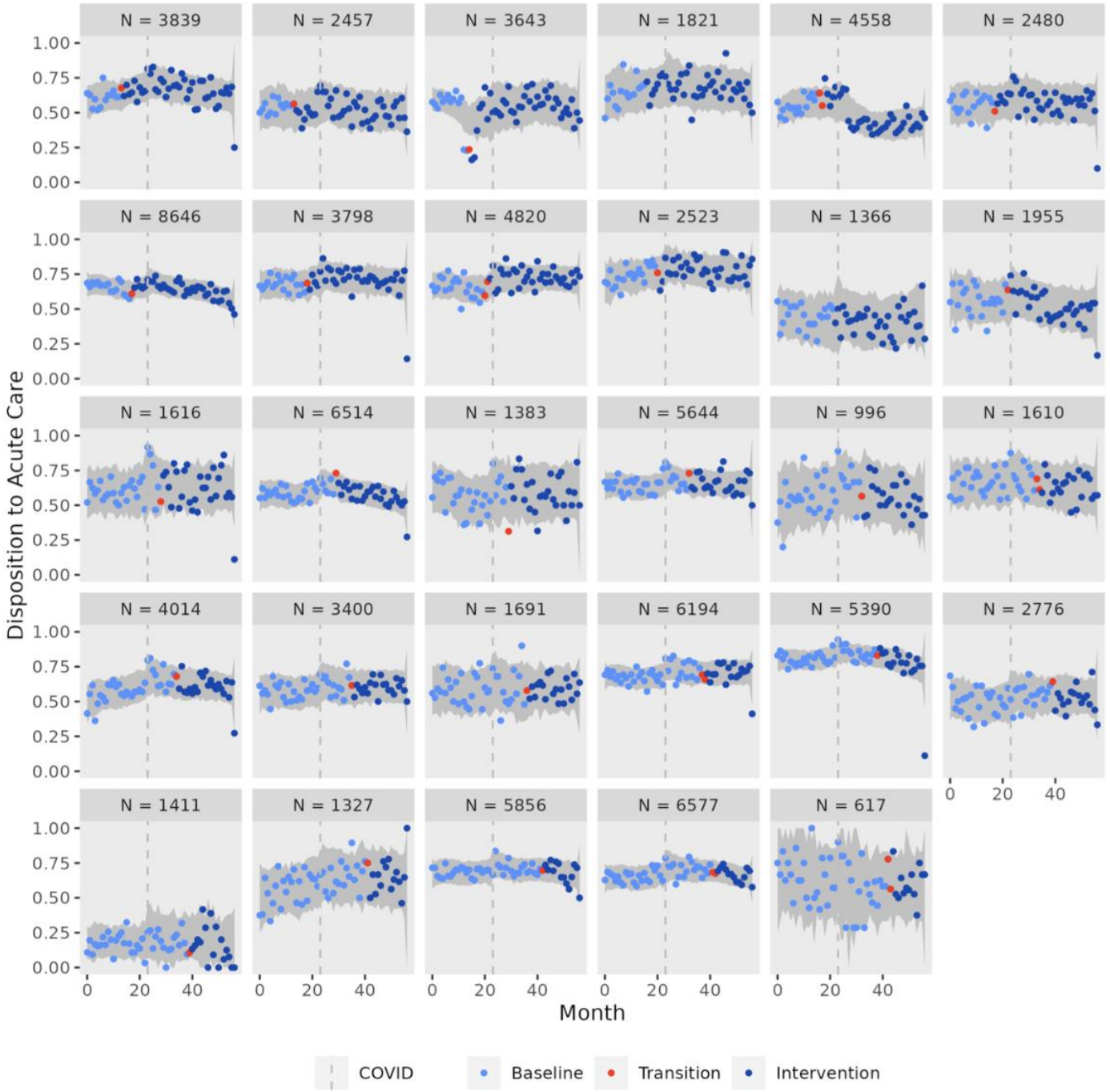
Results

Table 2: Model Results

	Pre-specified Model		Model adjusting for patient characteristics	
term	**OR**	**95% CI**	**OR**	**95% CI**
Intercept	1.30	[1.06 to 1.60]	0.42	[0.33 to 0.54]
COVID period	1.36	[1.20 to 1.56]	1.37	[1.20 to 1.57]
Intervention period	0.88	[0.76 to 1.03]	0.90	[0.77 to 1.04]
Post-Intervention period	1.03	[0.93 to 1.14]	1.04	[0.93 to 1.15]
COVID * Intervention period	1.18	[0.96 to 1.45]	1.17	[0.95 to 1.44]
COVID * Post-Intervention period	0.94	[0.84 to 1.05]	0.93	[0.83 to 1.04]
Age (10-year increments)			1.07	[1.06 to 1.09]
Black			0.82	[0.79 to 0.86]
Hispanic			0.79	[0.71 to 0.88]
Asian			1.10	[1.01 to 1.19]
Other race			0.93	[0.87 to 0.99]
Male			1.09	[1.06 to 1.12]
Gagne score			1.06	[1.06 to 1.07]

Results

Figure 1: Observed proportions by site and month



Results

- In this cluster randomized clinical trial, which was conducted at 29 US emergency departments (Eds) and included 98 922 initial visits, there was no difference in the rate of hospital admission in older adults with serious, life-limiting illness receiving care before (64.4%) vs after (61.3%) ED clinical staff receipt of a multicomponent primary palliative care intervention.

Surprises

- It was more challenging to implement the ED nurse training (1-hour online training) vs. the physicians/advance practice providers 4-hour in-person and/or Zoom training

- Approximately 1 in 3 emergency nurses reported that they will encounter barriers while engaging in serious illness conversation. Barriers included: human factors, time constraints, and challenges in the emergency work environment

- It is estimated that 1 trained EM provider will engage 19 seriously ill patients in serious illness conversations every year

- One year after active implementation of the final site, all sites (n=33) still had the BPA/Banner(s) active in the ED.
  - Only 7 sites out of 33 (21%) did not intend to continue to use the BPA/Banner in the future
  - 70% (23/33) sites stated they would recommend the Best Practice Alerts/Banner(s) to other EDs

Lessons Learned

- A sustainable training infrastructure needs to be in place
  - Ex: We did not have a mechanism to train/re-train new hires after active intervention period

- At teaching facilities collaborate with residency programs to ensure residents are also aware of provider facing best practice alerts and programs
  - Ex: We did not have the capacity to include residents in the intervention

- Engage IT leadership more than 6 months pre-implementation for building and reporting Best Practice Alerts

Future Plans

- LEading the Transformation of Alzheimer's and Dementia Care (ED- LEAD)
  - Leveraging PRIM-ER and other interventions, we are testing three interventions relevant to Persons Living With Dementia and their care partners who visit the ED:

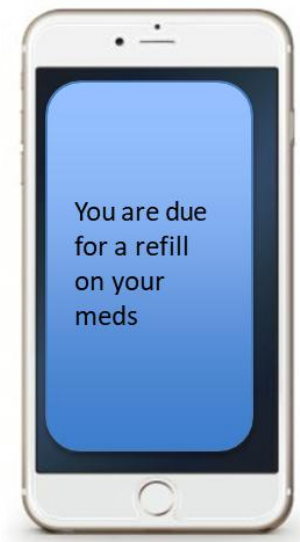
1. Emergency care redesign (UH3AT009844) of new and intentional workflows for emergency providers reinforced by digital alerts *(BPA component of PRIM-ER)*
2. A nurse-led telephonic care program (PCORI) that increased advance care planning and connected patients to hospice; and
3. Aa community paramedic-led structured coaching intervention (R01AG050504)

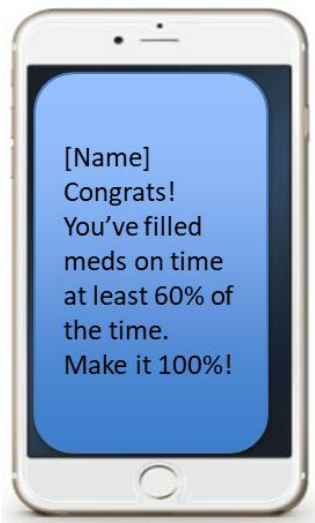
JAMA | Original Investigation

Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications

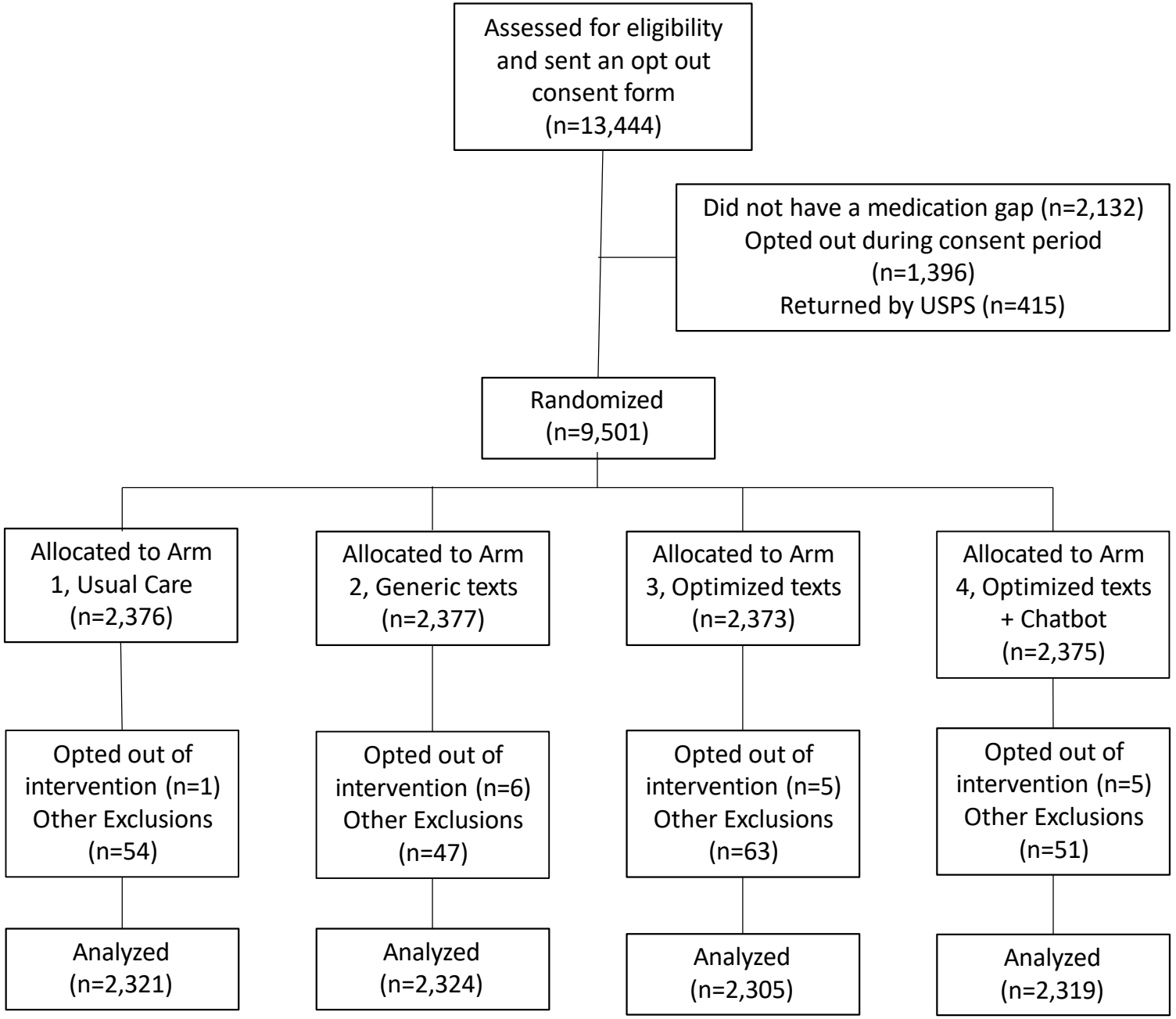
A Randomized Pragmatic Trial

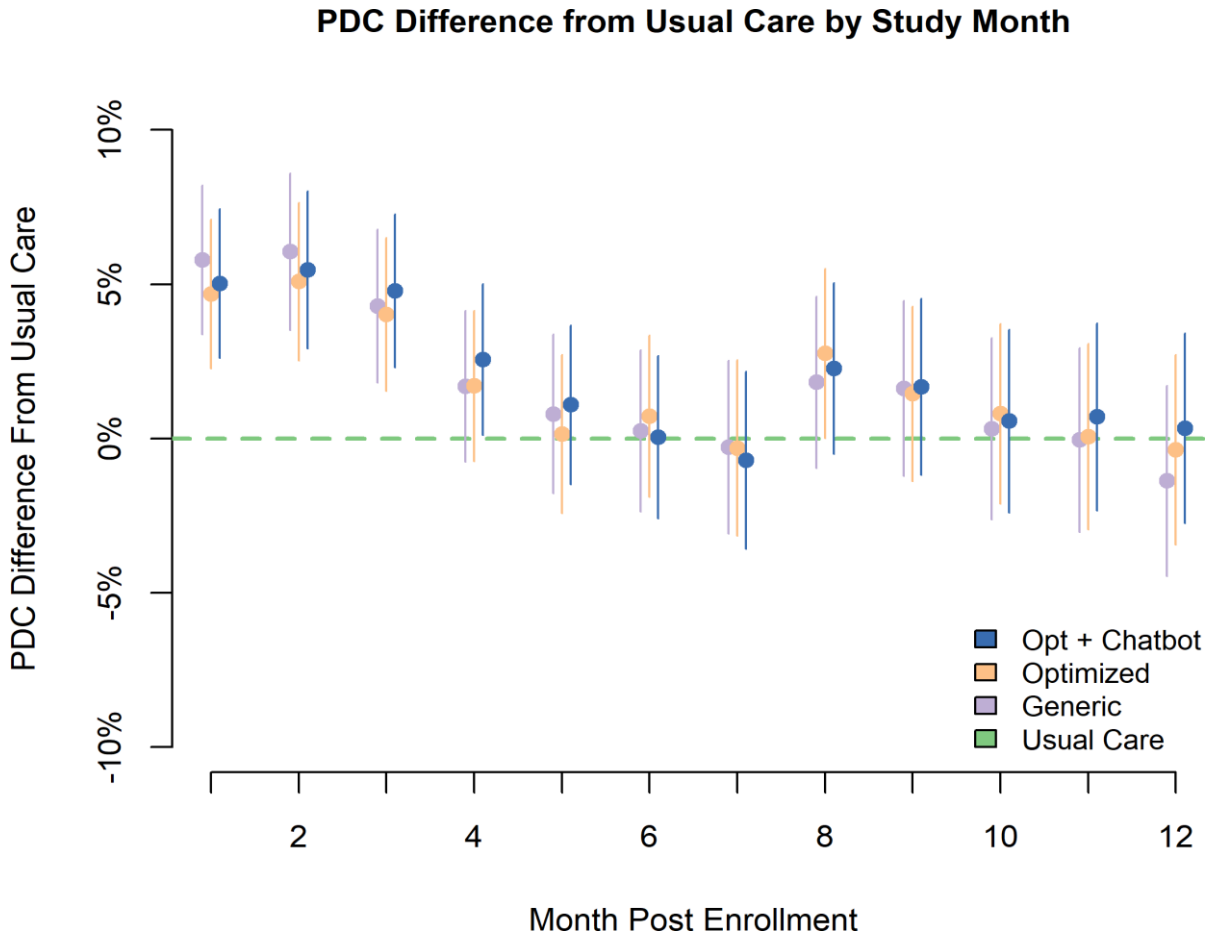
P. Michael Ho, MD, PhD; Thomas J. Glorioso, MS; Larry A. Allen, MD, MHS; Richard Blankenhorn, MSDA, BSF; Russell E. Glasgow, PhD; Gary K. Grunwald, PhD; Amber Khanna, MD; David J. Magid, MD, MPH; Joel Marrs, PharmD, MPH; Sylvie Novins-Montague, BA; Steven Orlando, PharmD; Pamela Peterson, MD, MSPH; Mary E. Plomondon, PhD; Lisa M. Sandy, MA; Joseph J. Saseen, PharmD; Katy E. Trinkley, PharmD, PhD; Shawni Vaughn, MAS; Joy Waughtal, MPH; Sheana Bull, PhD





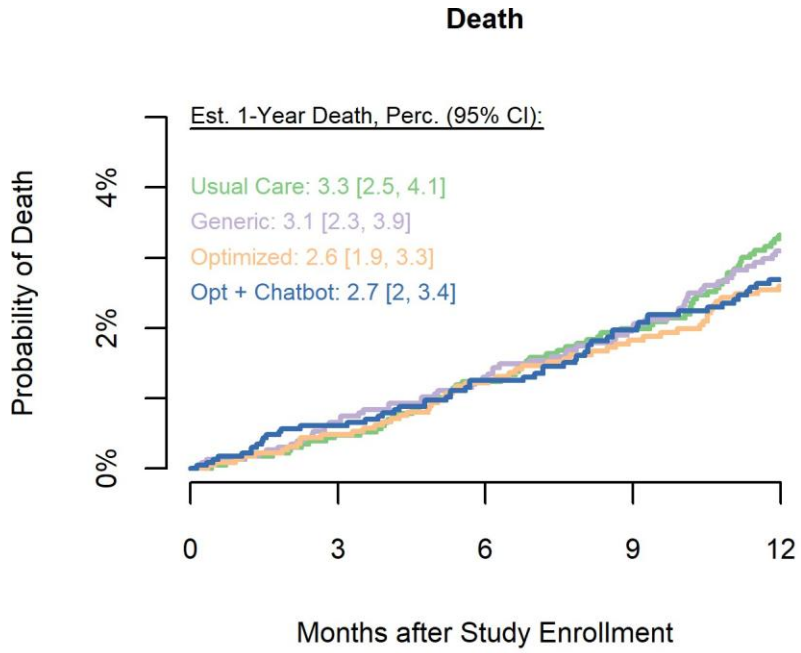
Patient flow

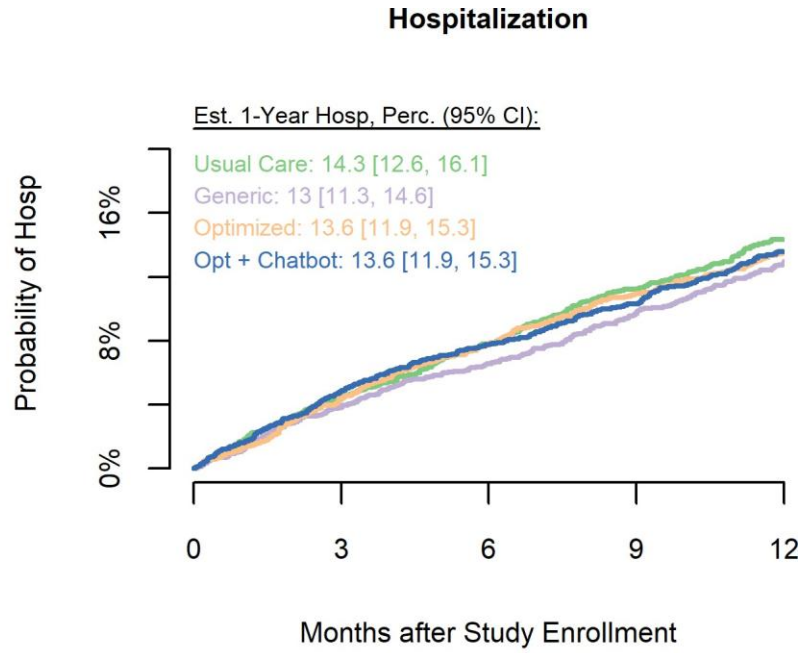


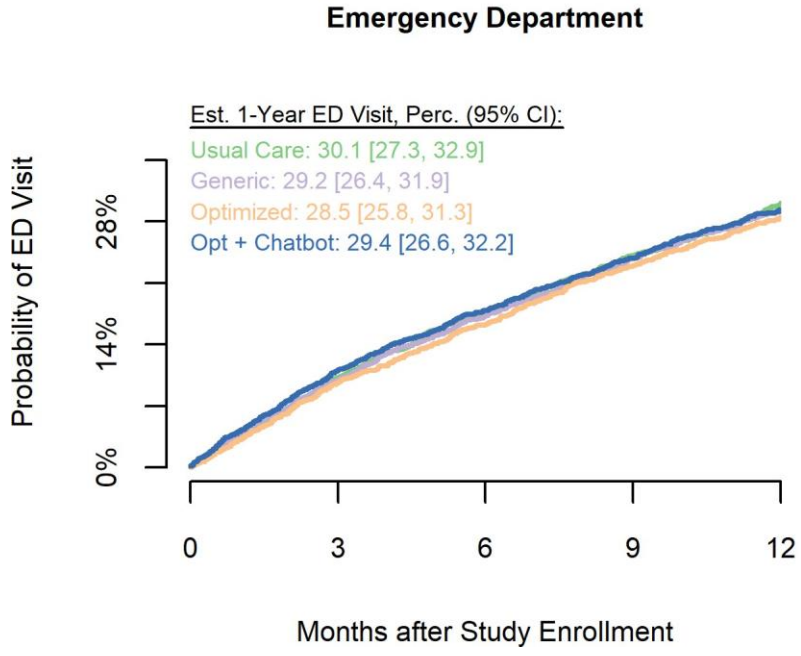


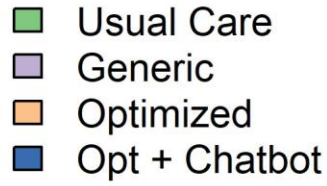
	Usual Care	Generic	Optimized	Opt + Chatbot
PDC at 3 months	56.2%	61.4%	61.1%	61.6%
PDC at 12 months	60.6%	62.0%	62.3%	63.0%

Clinical Events









Lessons Learned

- Opt-out enrollment approach is an option for low-risk studies
- Adherence interventions should be multi-modal and bi-directional
- Defining outcome measures that are sensitive to the intervention
- Consideration of pros/cons of health system integration
- Next steps: Conducting Chat 4 Heart Health study

Pragmatic trial of higher vs lower serum phosphate targets in patients undergoing hemodialysis

Rishi Chakraborty
DCRI, Duke University

HiLo: A Pragmatic, Randomized Trial of Phosphate Management for Patients on Maintenance Hemodialysis

Setting & Participants

HiLo

Pragmatic, cluster-randomized trial

4,400 patients receiving thrice-weekly hemodialysis in 80-120 dialysis facilities

Intervention

'Hi' phosphate target (≥6.5 mg/dl)

vs

'Lo' phosphate target (<5.5 mg/dl)

Follow-up: 27-45 months

–

Interventions to reach phosphate targets at the discretion of the dietitians & providers

Novel Design Features

- Extensive stakeholder engagement with patients, dietitians, nephrologists
- Hierarchical composite outcome of all-cause mortality & hospitalizations
- Pragmatic trial with liberal eligibility criteria
- Electronic informed consent (eConsent)
- Real-world data collection from EHR

CONCLUSION: HiLo will address the question of what serum phosphate target to use in hemodialysis while advancing methods for pragmatic clinical trials in nephrology.

Daniel L. Edmonston, Tamara Isakova, Laura M. Dember, et al (2020)

@AJKDonline | DOI: 10.1053/j.ajkd.2020.10.008

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

Study Overview

- **Target Enrollment**

  Cluster: 4400 participants at 100-150 dialysis centers across the US.

  Individual: 3800 participants at 100-150 dialysis centers across the US.

- **Study Population**

  Adults > 18 years with end stage renal disease (ESRD) undergoing three-times-weekly in-center hemodialysis for at least three months

- **Dialysis Providers**

  DaVita, Inc

  University of Utah (later acquired by DaVita)

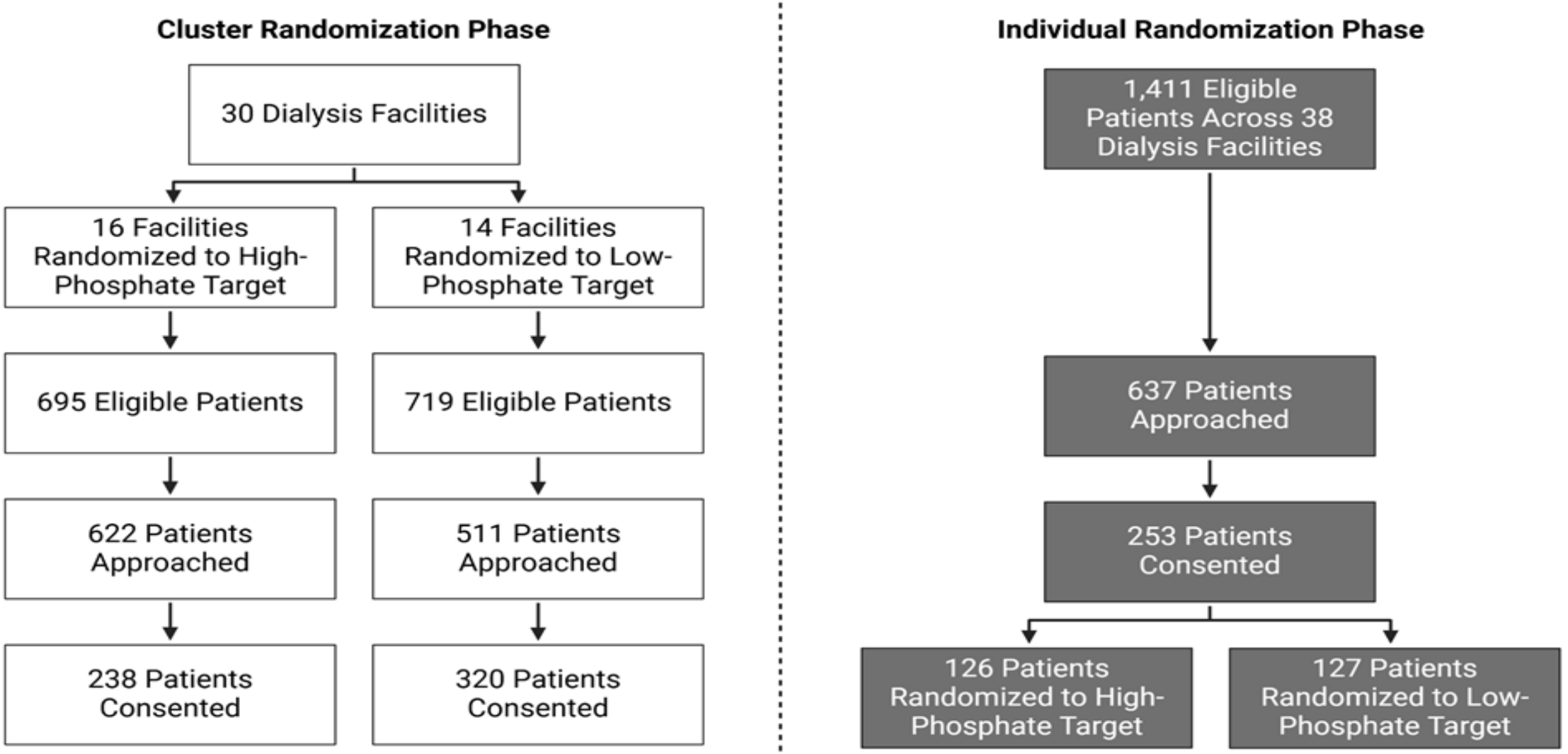
Timeline Overview

- **Original Study Design (starts: November 2019 protocol)**
  Pragmatic, cluster-randomized, open-label, non-inferiority outcomes trial.

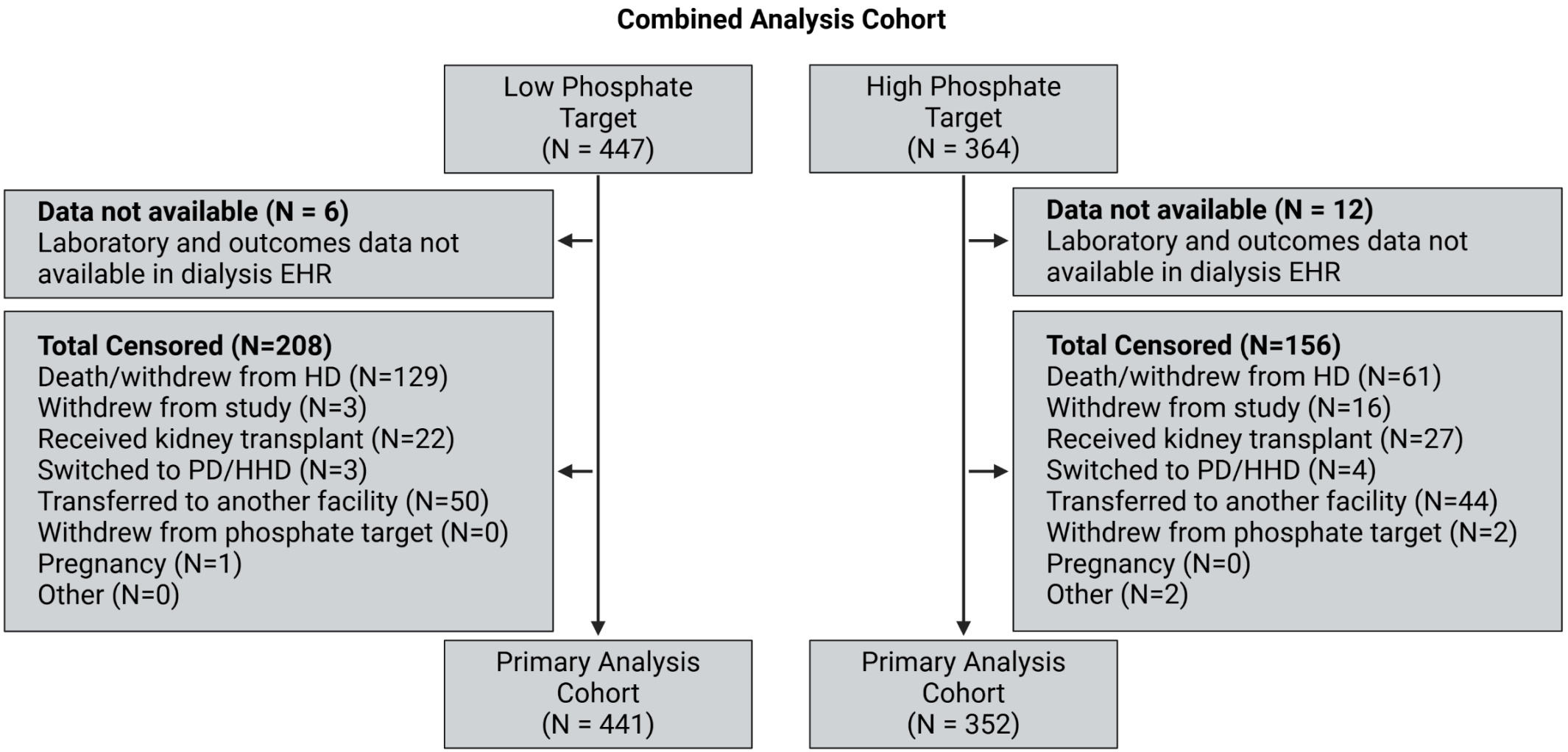
- **Modified Study Design (starts: September 2021 protocol)**
  Pragmatic, open-label, multicenter, clinical outcomes trial with individual-level randomization.

- **Study Ends: November 2023**

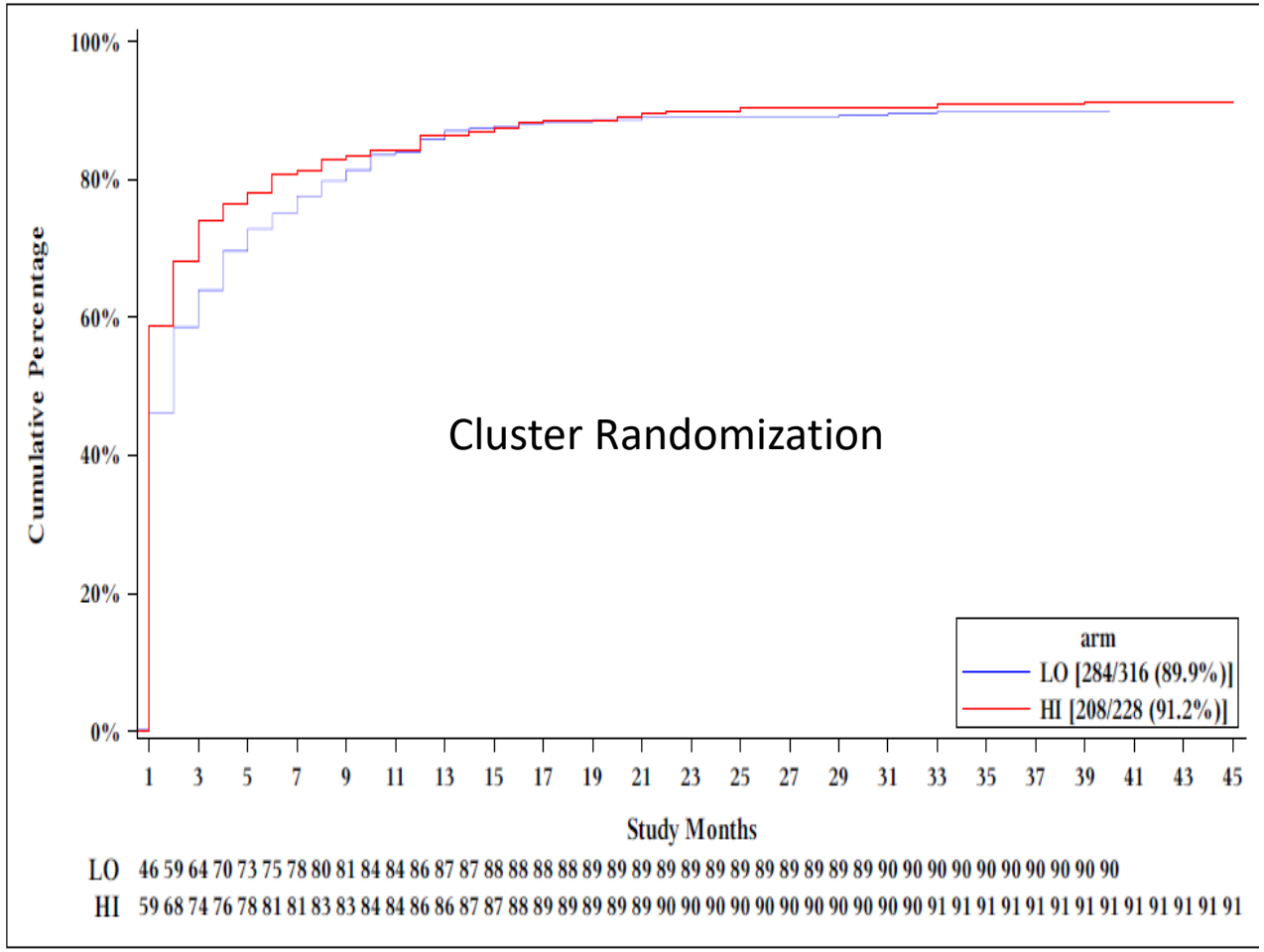
Enrollment

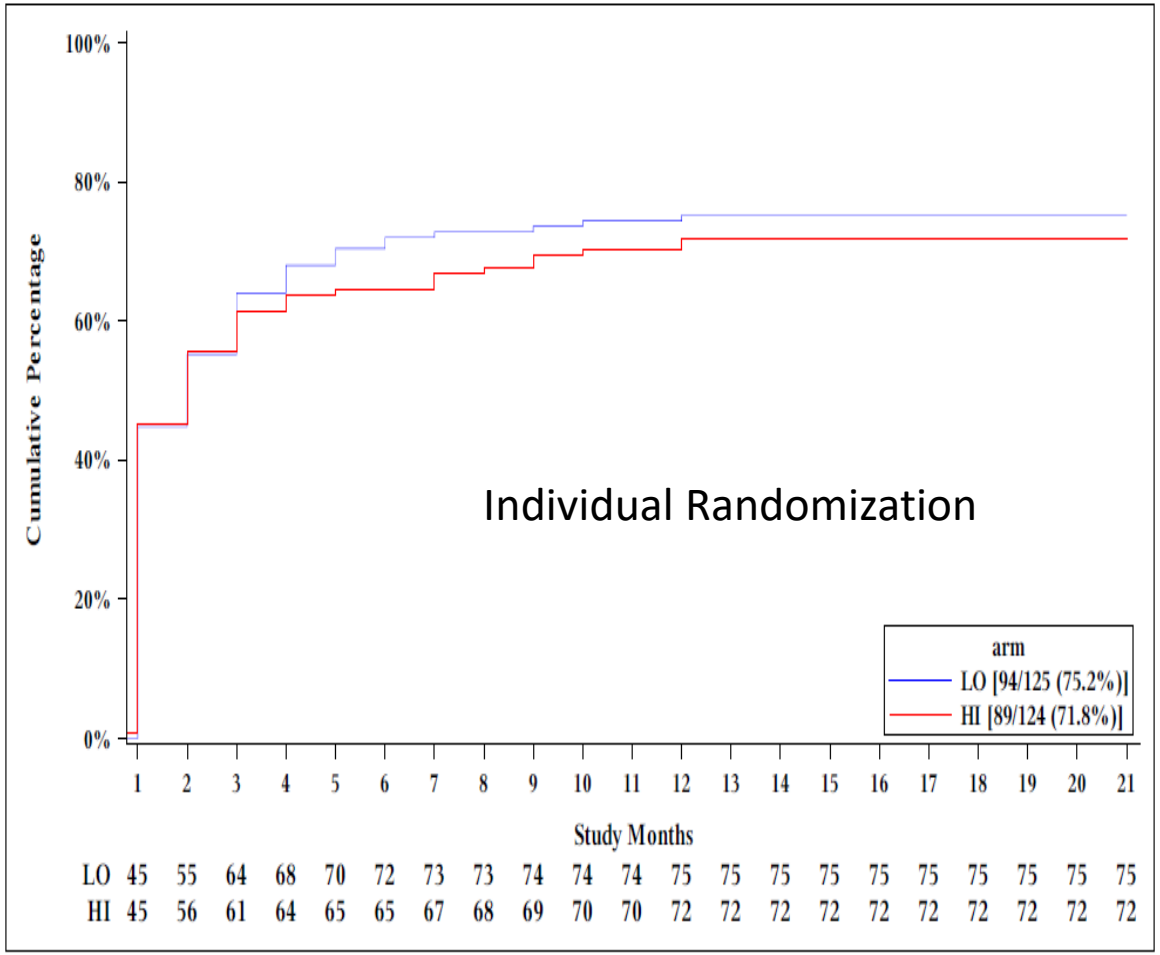

Cluster Randomization Phase
30 Dialysis Facilities
16 Facilities Randomized to High-Phosphate Target
14 Facilities Randomized to Low-Phosphate Target
695 Eligible Patients
719 Eligible Patients
622 Patients Approached
511 Patients Approached
238 Patients Consented
320 Patients Consented
Individual Randomization Phase
1,411 Eligible Patients Across 38 Dialysis Facilities
637 Patients Approached
253 Patients Consented
126 Patients Randomized to High-Phosphate Target
127 Patients Randomized to Low-Phosphate Target

Enrollment


Combined Analysis Cohort
Low Phosphate Target (N = 447)
High Phosphate Target (N = 364)
Data not available (N = 6)
Laboratory and outcomes data not available in dialysis EHR
Data not available (N = 12)
Laboratory and outcomes data not available in dialysis EHR
Total Censored (N=208)
Death/withdrew from HD (N=129)
Withdrew from study (N=3)
Received kidney transplant (N=22)
Switched to PD/HHD (N=3)
Transferred to another facility (N=50)
Withdrew from phosphate target (N=0)
Pregnancy (N=1)
Other (N=0)
Total Censored (N=156)
Death/withdrew from HD (N=61)
Withdrew from study (N=16)
Received kidney transplant (N=27)
Switched to PD/HHD (N=4)
Transferred to another facility (N=44)
Withdrew from phosphate target (N=2)
Pregnancy (N=0)
Other (N=2)
Primary Analysis Cohort (N = 441)
Primary Analysis Cohort (N = 352)

Cumulative Distribution of Participants Reaching their Phosphate Target Range for the First Time





Conclusions

- The primary hierarchical composite outcome did not differ between groups (win ratio for Hi versus Lo targets was 0.97; 95% confidence interval, 0.55-1.71).

- Although insufficient enrollment and inadequate phosphate separation between groups preclude inferences about the effects of phosphate targets on clinical outcomes, features of HiLo can inform future trial design in maintenance hemodialysis populations.

Higher versus Lower Phosphate Targets for Patients Undergoing In-Center Hemodialysis: A Randomized Controlled Trial (submitted to Journal of the American Society of Nephrology in May 2025)

Discussion

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®