TiME Trial Overview

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AcademyHealth Annual Research Meeting
June 3, 2019

TiME

Penn Medicine
Perelman School of Medicine
University of Pennsylvania Health System

Hemodialysis as a Setting for Pragmatic Trials

- Highly accessible study population with frequent, regular clinical encounters
- Granular and uniform data collection as part of routine clinical care
- Infrastructure of dialysis provider organizations that allows for centralized implementation approach
- High event rates

Many Questions about Fundamental Aspects of Care

- Duration of hemodialysis sessions?
- Blood pressure target?
- Phosphorus target?
- Hemoglobin target?
- Preventive health care?
- Anticoagulation for atrial fibrillation?
- Dialysis solution electrolyte concentrations?

Trial Hypothesis

For thrice-weekly maintenance hemodialysis, treatment with session durations >4 hours will improve outcomes compared with usual care.

Slower removal of fluid will result in:

- Less intra-dialytic hypotension
- Less myocardial “stunning”
- More consistent attainment of target weight

Design and Implementation Approach

- Setting
  - 266 outpatient dialysis units operated by two large US dialysis provider organizations
- Design
  - Cluster randomized
  - Intervention: default hemodialysis session duration ≥4.25 hours
  - Usual Care: no trial-driven approach to session duration
- Outcomes
  - Primary: mortality
  - Secondary: hospitalizations, quality of life

Design and Implementation Approach

- Consent
  - Waiver of requirement for informed consent
  - Patients could opt out of sharing data
- Eligibility Criteria
  - Age ≥18 years
  - Dialysis initation within the past 120 days
  - Ability to provide consent for clinical care
- Implementation
  - Fully embedded in clinical care delivery
  - No on-site research personnel
  - Nephrologists prescribe the session duration
  - Complete reliance on clinically acquired data

Active Bathing to Eliminate Infection Project

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Disclosures

- Conducting clinical studies in which participating hospitals and nursing homes receive contributed antiseptic products from Stryker, Molnlycke, 3M, Xttrium, Clorox, and Medline
- Companies contributing product have no role in design, conduct, analysis, or publication

ABATE Infection Trial:
Rationale

- Hospital-associated infections are serious preventable events
- Prior ICU trial (REDUCE MRSA Trial) evaluated universal antiseptic soap and nasal antibiotic ointment vs routine care
  - Reduced Methicillin Resistant *Staph aureus* by 37%
  - Reduced all-cause bloodstream infection by 44%
- Antiseptic bathing is now standard of care in ICUs
- Is there a benefit for antiseptic bathing outside of ICUs?

ABATE Infection Project

Design and Intervention

Trial Design

- Cluster randomized trial with HCA Healthcare
- 53 hospitals, 194 adult non critical care units

Arm 1: Routine Care

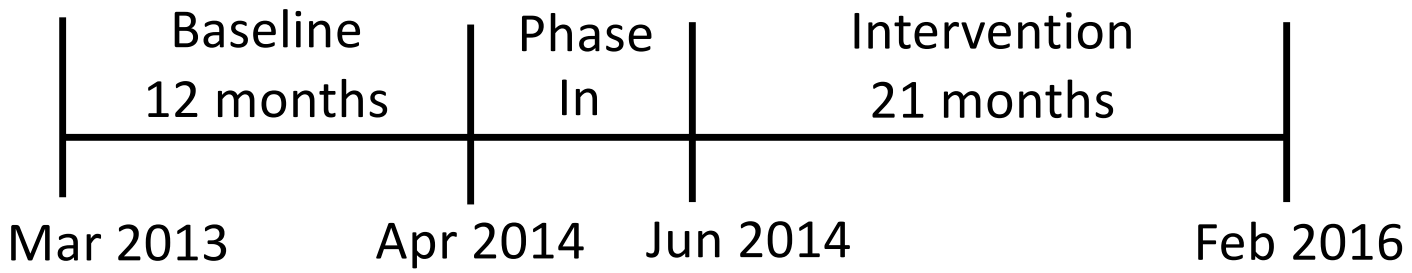
- Routine policy for showering/bathing

Arm 2: Decolonization

- Daily 4% rinse off chlorhexidine (CHG) for showers
- 2% leave-on CHG for bed baths
- Nasal antibiotic mupirocin x 5 days if MRSA+

Outcomes and Study Period

- **Primary Outcome**
  - Any MRSA or VRE isolate attributed to unit
- **Key Secondary Outcome**
  - All cause bloodstream infection
- **339,904 patients, 1,294,153 patients days (intervention)**



Huang SS Lancet 2019;393(10177):1205-1215

Results: Decolonization in General Wards

- No overall population benefit, unlike ICU trials
  - Lower risk and smaller effect size
  - 8.7% for MDROs, 6.2% bloodstream infection (P=NS)
- Benefit seen in **higher risk patients with lines and devices**
  - 32% reduction in MRSA and VRE clinical cultures
  - 28% reduction in all pathogen bloodstream infection
  - 10% of population, but a third of MRSA+VRE cultures
  - 10% of population, but 60% of bloodstream infections

Huang SS Lancet 2019;393(10177):1205-1215

Health System Partnership

- HCA Healthcare Corporate Leadership
- Compliance and Regulatory Affairs
- Clinical Services Group
- Infection Prevention
- Information Technology
- Pharmacy and Supply Chain
- Unit Directors and Managers
- Laboratory and Microbiology

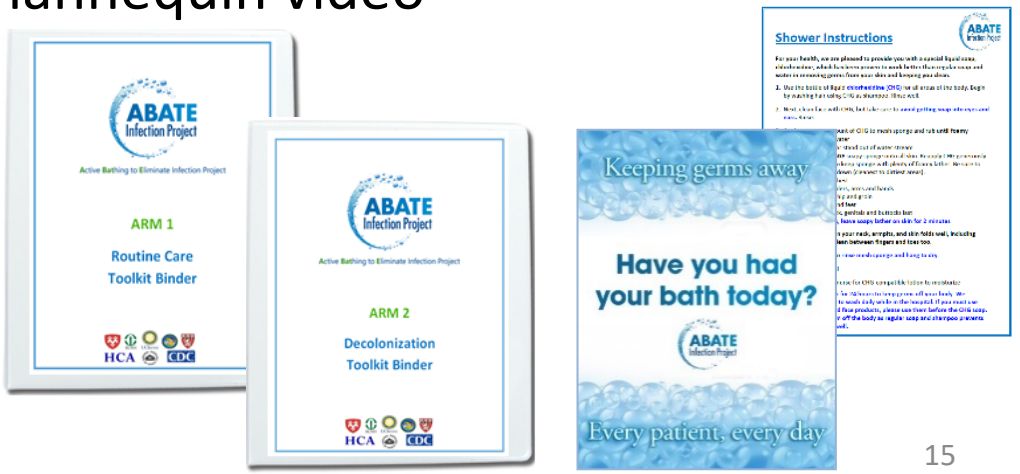
Recruitment & IRB Process

- **53 hospitals recruited in 11 weeks**
  - Leveraged HCA communication
  - Calls for Division CMOs/CNOs, infection prevention
  - CEO attestation letters

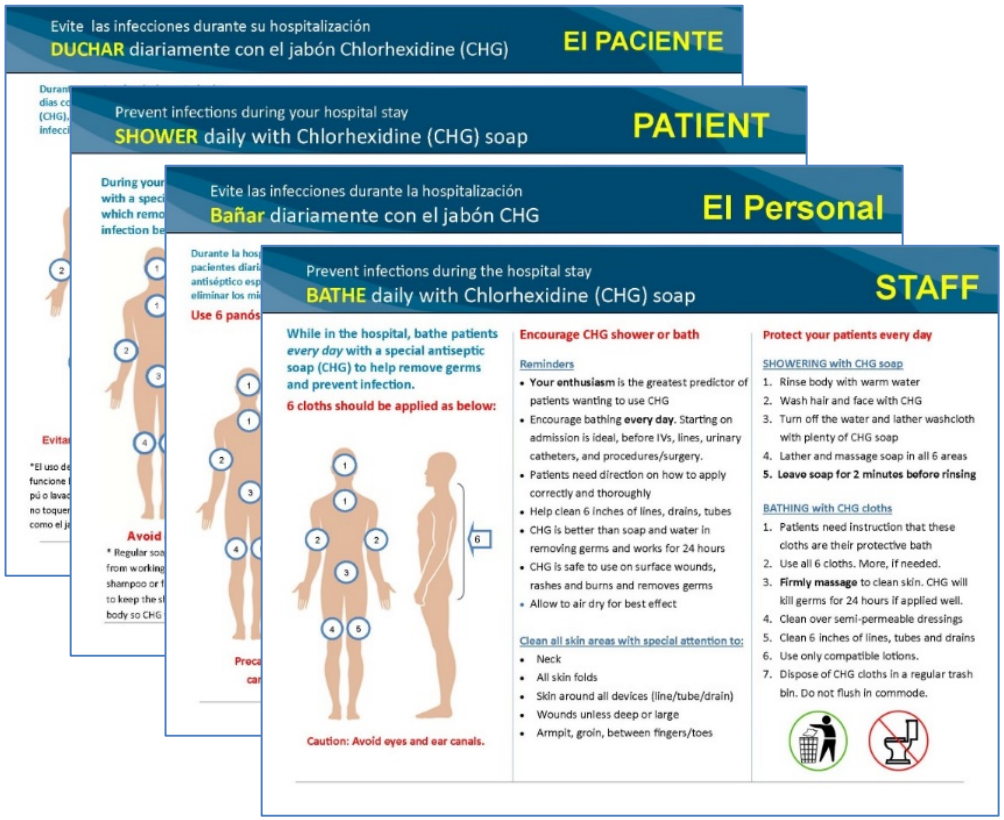
- **Centralized IRB (Harvard)**
  - 52 of 53 hospitals ceded within 5 months
  - One hospital's IRB provided prisoner oversight
  - HCA Compliance developed scope relevant training
  - Waiver of informed consent

Central Coordination

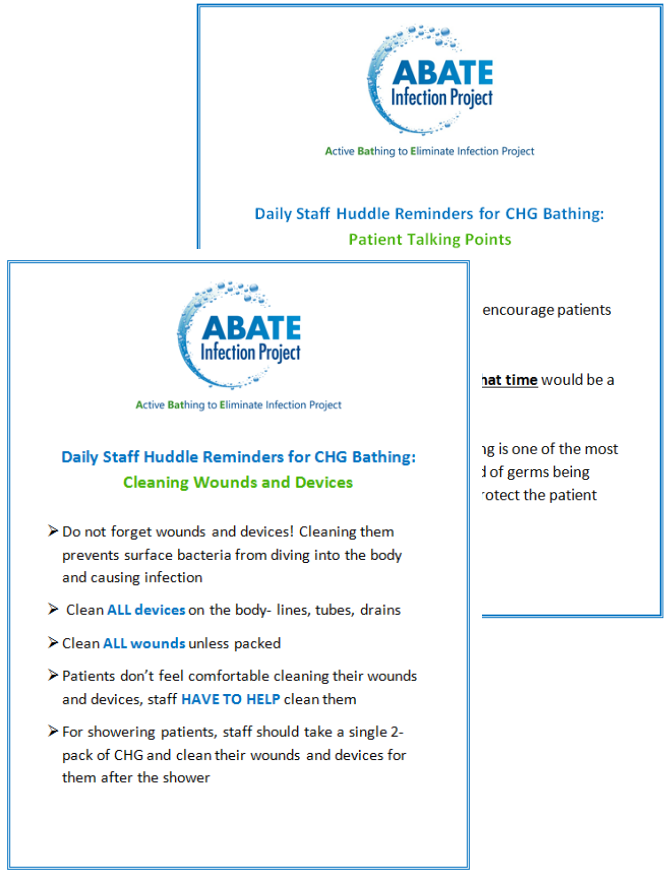
- **Coaching Calls (both arms)**
- **Trial email and help line (11,200 inquiries fielded)**
- **Assessed skin product compatibility with CHG**
- **Educational Materials**
  - Computer based training: 14,000 RN training sessions
  - 10 minute bathing mannequin video
  - 239 toolkit binders
  - 3,500 posted clings



Handouts

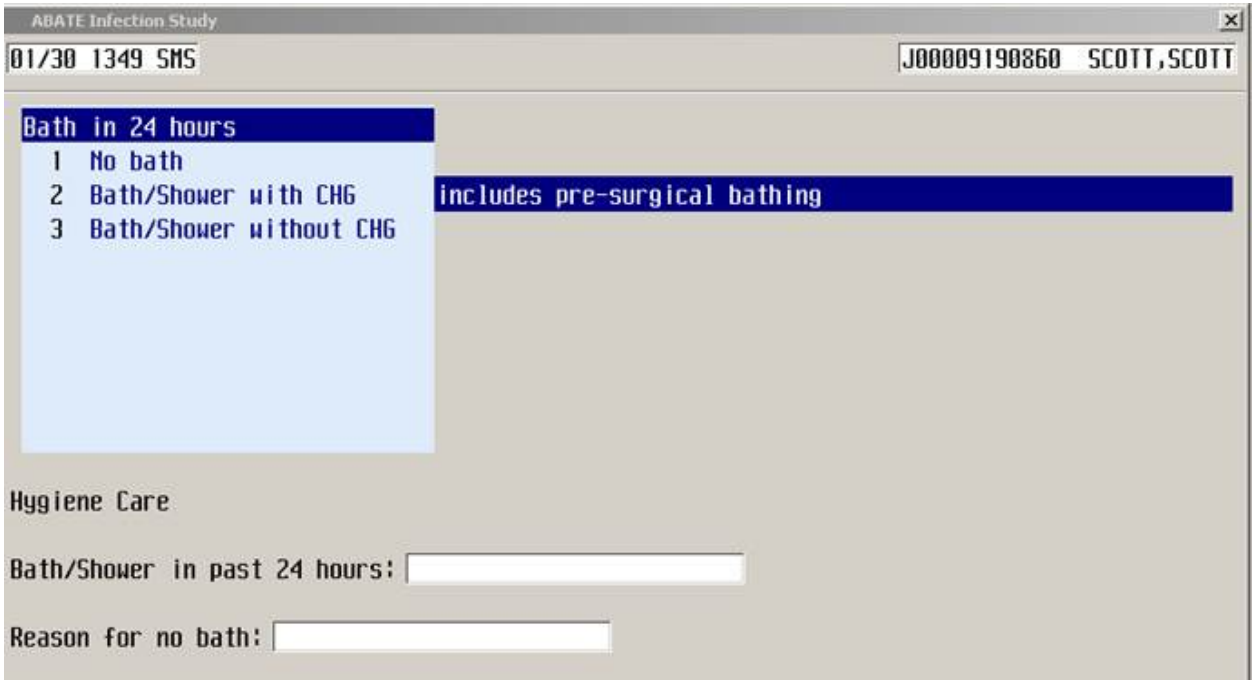


Arm 2 Instructional Handouts Provided in English and Spanish



Arm 2 Huddle Documents Covering 14 Topics

Nursing Documentation for ABATE



Number of Query Documentations

Arm	Phase-In April - May 2014	Intervention June 2014 - February 2016
1	71,456	619,106
2	104,686	984,136

Quarterly Staff and Patient Assessments

Hospital Name: _____ Unit Name: _____

HCA
Hospital Corporation of America™

Skills Assessment:
CHG Cloth Observation Checklist

Please complete for **THREE** different staff **per unit**

Individual Giving CHG Bath

Please indicate who performed the CHG bath.

☐ Nursing Assistant (CNA) ☐ Nurse ☐ Other: _____

Observed CHG Bathing Practices

Please check the appropriate response for each observation.

☐ Y	☐ N		Patient received CHG cloth bathing handout
☐ Y	☐ N		Patient told that bath is a no rinse cloth that provides protection from germs
☐ Y	☐ N		Provided rationale to the patient for not using soap at any time while in unit
☐ Y	☐ N		Massaged skin *firmly* with CHG cloth to ensure adequate cleansing
☐ Y	☐ N		Cleaned face and neck well
☐ Y	☐ N		Cleaned between fingers and toes
☐ Y	☐ N		Cleaned between all folds
☐ Y	☐ N	☐ N/A	Cleaned occlusive and semi-permeable dressings with CHG cloth
☐ Y	☐ N	☐ N/A	Cleaned 6 inches of all tubes, central lines, and drains closest to body
☐ Y	☐ N	☐ N/A	Used CHG on superficial wounds, rash, and stage 1 & 2 decubitus ulcers
☐ Y	☐ N	☐ N/A	Used CHG on surgical wounds (unless primary dressing or packed)
☐ Y	☐ N		Allowed CHG to air-dry / does not wipe off CHG
☐ Y	☐ N		Disposed of used cloths in trash /does not flush

Query to Bathing Assistant/Nurse

1. How many cloths were used (1 cloth set = 6 cloths, 1 cloth set plus 1 single pack = 8 cloths)

_____

2. If more than 1 cloth set (6 cloths) was used, provide reason.

_____

3. Do you reapply CHG after an episode of incontinence has been cleaned up?

_____

4. Are you comfortable applying CHG to superficial wounds, including surgical wounds?

_____

5. Are you comfortable applying CHG to lines, tubes, drains and non-gauze dressings?

_____

6. Do you ever wipe off the CHG after bathing?

_____

Email to ABATEStudy@gmail.com or fax to (949) 824-3985

 # completed: 1,469

Hospital Name: _____ Unit Name: _____

HCA
Hospital Corporation of America™

Skills Assessment:
CHG Showering – Patient Self-Bathing

Please complete for **THREE** different patients **per unit**

Please record patient responses after the patient showered with CHG liquid.

Questions

1. Were you provided a handout with instructions on how to apply the CHG liquid in the shower?
   ☐ Y ☐ N
2. Were you told that CHG kills germs better than regular soap and water?
   ☐ Y ☐ N
3. Did you use the mesh sponge to apply the CHG?
   ☐ Y ☐ N

4. Did you soap up twice with CHG before rinsing?
   ☐ Y ☐ N
5. Did you leave the CHG on your skin for 2 minutes before rinsing off?
   ☐ Y ☐ N
6. Were you told NOT to use other bathing soaps or lotions while in this unit?
   ☐ Y ☐ N
7. Were you told to bathe or shower daily with CHG while in this unit?
   ☐ Y ☐ N
8. Did you or an assistant clean your lines, tubes, and/or drains with a CHG cloth after showering?
   ☐ Y ☐ N ☐ N/A
9. Did you or an assistant clean your wounds with a CHG cloth after showering?
   ☐ Y

 # completed: 1,251

Competing Interventions

- New/proposed interventions evaluated by Steering Committee to check for conflict with trial outcomes

Arm	Proposed Interventions	Allowed	Not Allowed (Conflicting)
Routine	83	47 (57%)	36 (43%)
Decolonization	102	73 (72%)	29 (26%)
Division	9	7 (78%)	2 (22%)
Corporate	2	2 (100%)	0 (0%)
Total	**196**	**129 (66%)**	**67 (34%)**

*Additional 8 (4%) interventions reported, but withdrawn

Post-Randomization Drop Out

- **5 of 53 Hospitals Dropped Out**
  - 1 divested from HCA
  - 1 had single participating unit close
  - 3 competing interventions
    - Arm 1 (Routine Care) – 2 for CHG bathing
    - Arm 2 (Decolonization) – 1 for enhanced cleaning

Centralized Data Warehouse

- **Patient Level Data**
  - Location and census data
  - Diagnostic/procedure codes
  - Pharmacy data
  - Microbiology data
  - Nursing query

20 million records
474 million data elements

PROVEN

PRagmatic Trial of Video Education in Nursing Homes

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Vincent Mor, PhD
Angelo Volandes, MD, MPH

4UH3AG049619-02

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Institute for Aging Research
Hebrew SeniorLife

PROVEN: Objective

- To conduct a pragmatic cluster RCT of an Advance Care Planning video intervention in NH patients with advanced comorbid conditions in two NH healthcare systems

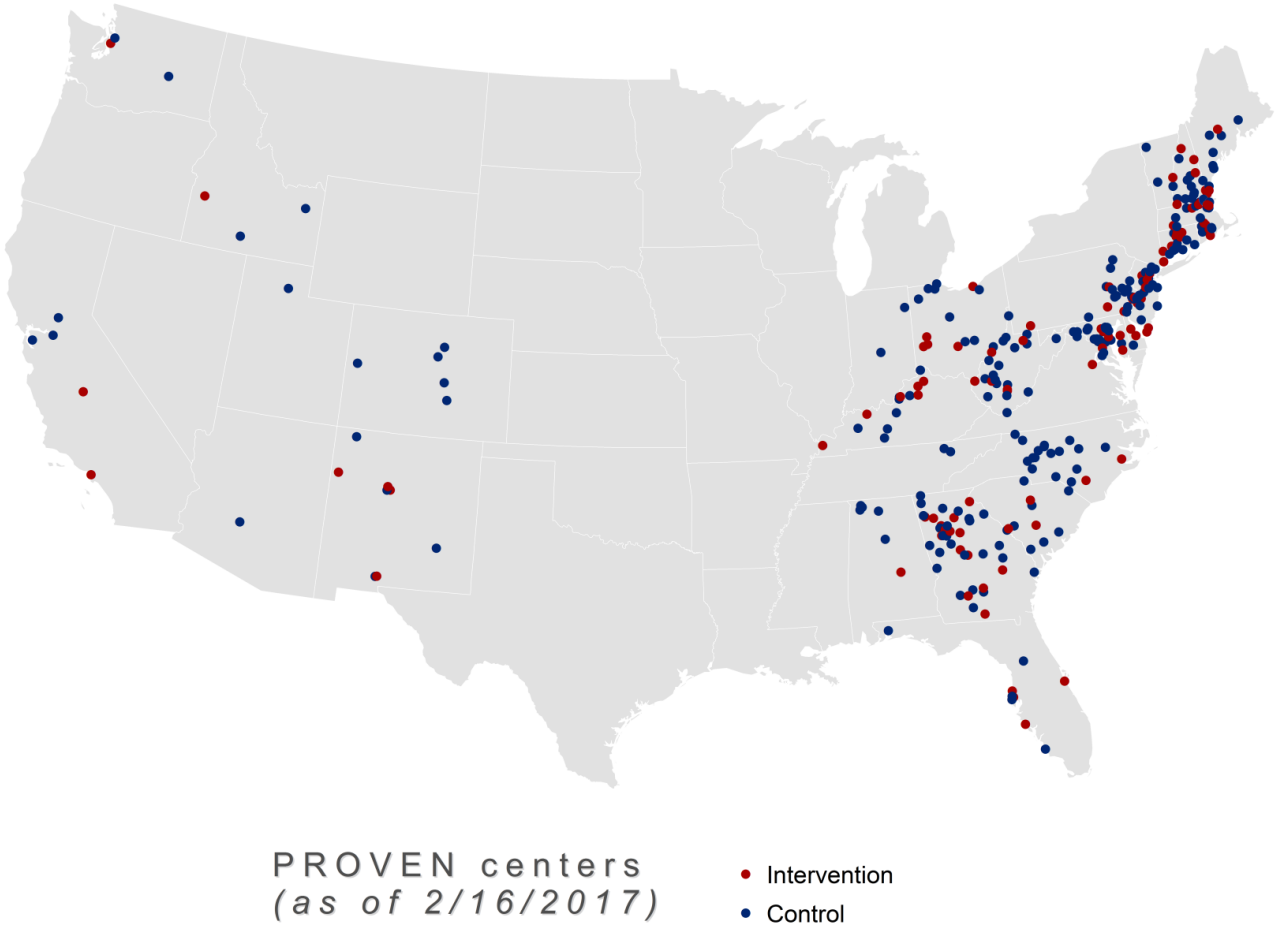
Background: ACP videos

- Options for care with visual images
- Broad goals of care
  - Life prolongation, limited, comfort
- Specific conditions/treatments
- Adjunct to counseling
- 6-8 minutes
- Multiple languages

PROVEN: Intervention NHs

- 24 month accrual; 12 month follow-up
- Suite of 5 ACP videos
  - Goals of Care, Advanced Dementia, Hospitalization, Hospice, ACP for Healthy Patients
- Offered facility-wide
  - All new admits, at care-planning meetings for long-stay, readmission
- Flexible (who, how, which video)
- Tablet devices, internet via URL and password
- Training: corporate level, webinars, toolkit

Distribution of PROVEN NHs



PROVEN: Primary Outcome

- Number of hospital transfers*/person-days alive among Fee-For-Service Medicare beneficiaries >=65 years old who are in a NH >=90 days ("long-stay") and who have EITHER advanced dementia or advanced congestive heart failure/chronic obstructive lung disease
- This is our **target** cohort.

* Transfers include hospital admissions, Observation Stays & ED visits.

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Comparative Effectiveness Pragmatic Trial of Hi Dose vs. Standard Dose Influenza Vaccine in US Nursing Homes

Vincent Mor, Ph.D.

Florence Grant Pirce Professor of Health Services, Policy & Practice

Research Scientist, Providence VAMC

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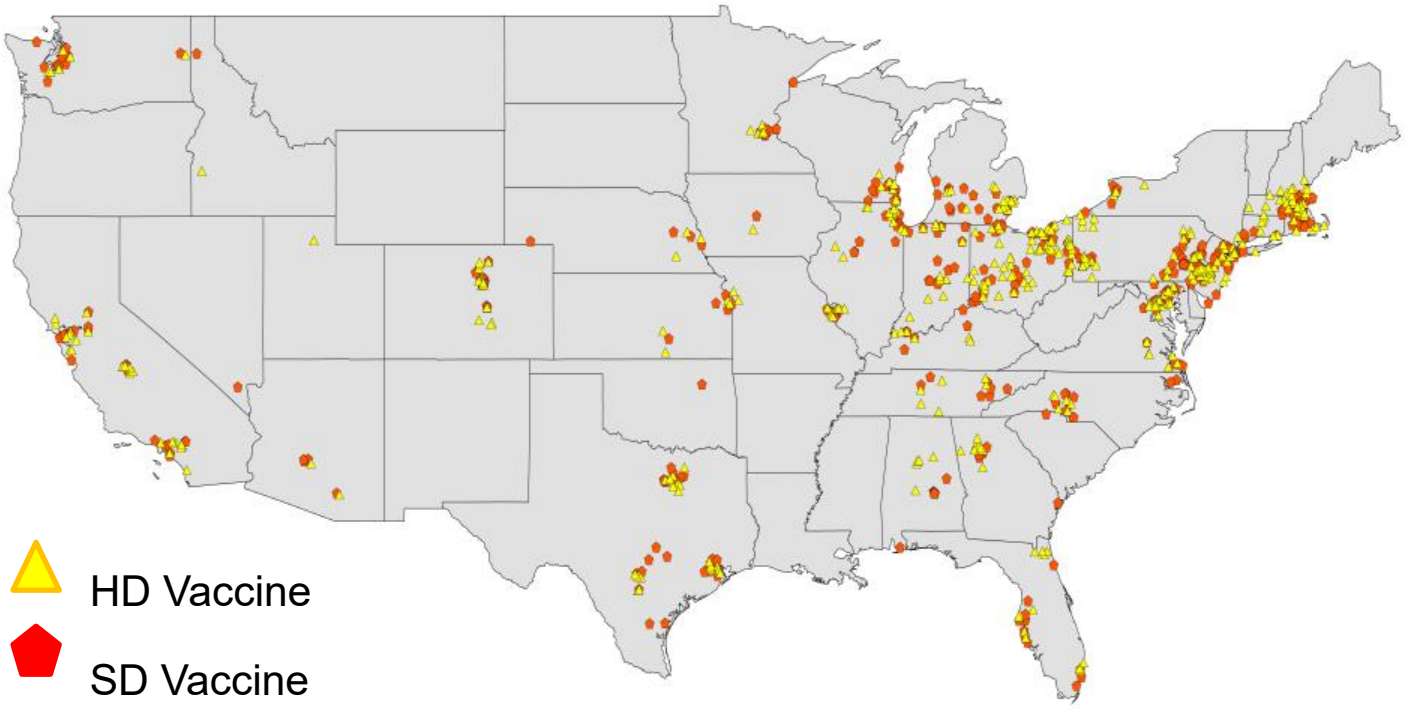
Pragmatic Cluster RCT of HD in Nursing Homes

- Recruit NHs in areas adjacent to 122 cities in CDC Influenza Surveillance System
- Use federally mandated nursing home resident MDS assessment to **identify** permanent NH residents with selected demographic and functional characteristics AND to measure outcomes
- Use Medicare hospital claims to **measure outcome** of hospitalization for influenza (pneumonia and influenza [P&I]) and cardiovascular exacerbations of influenza; **Fee for Service ONLY; Medicare Advantage Dropped; no claims data**

Participating NHs by State (n=823)



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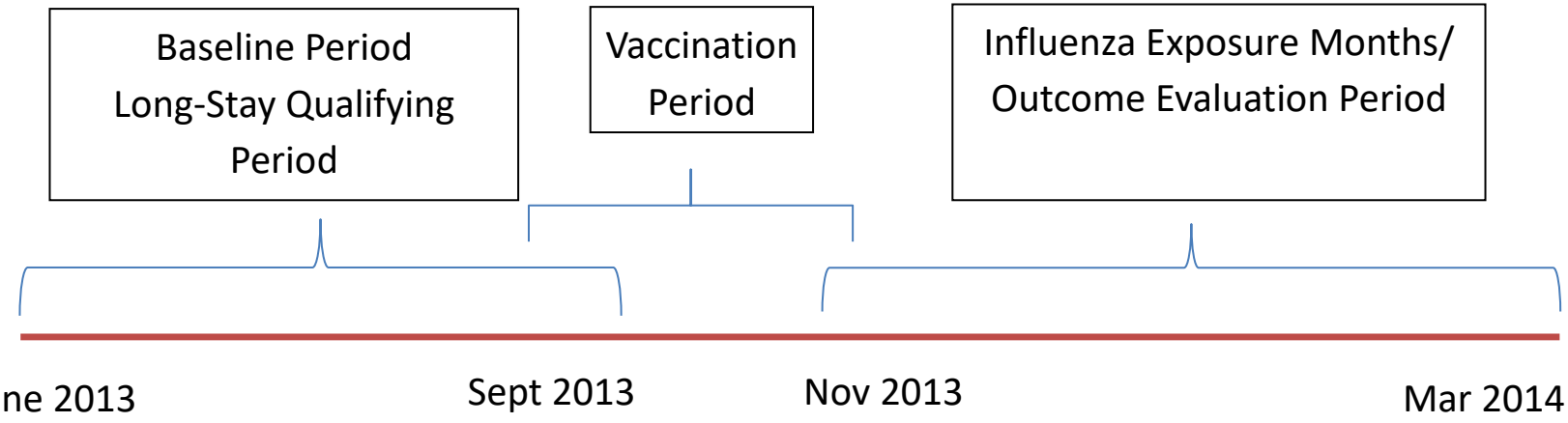
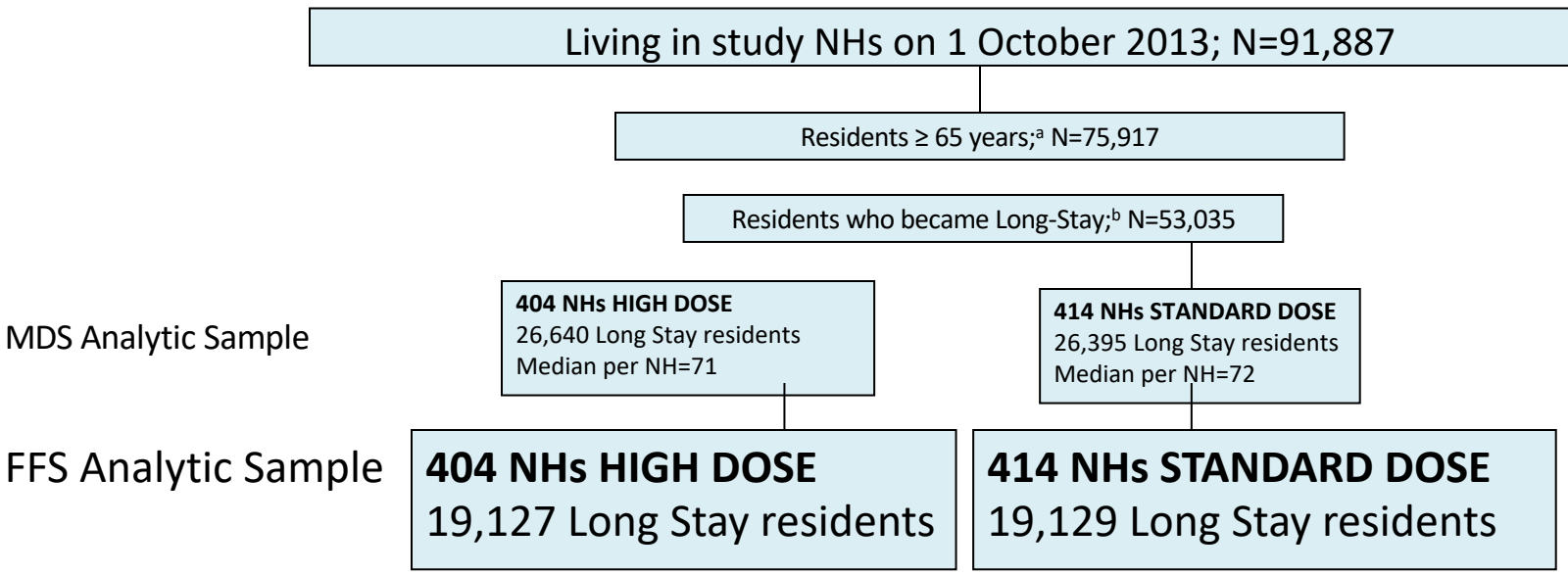
Patient Selection



Cohort Selection, 2013-2014

(ALL Long-stay NH residents >65 years)



[a] Residents who were 65 years old on October 1, 2013.

[b] Long-stay residents are NH residents with quarterly and annual MDS assessments. Residents who were discharged from the nursing home to: 1) the community, 2) inpatient rehabilitation facility, 3) hospice, 4) other location, or 5) as dead in the baseline period are excluded from the analytical sample. Residents are included if they were discharged to another nursing home, acute hospital, psychiatric hospital, or MR/DD facility.

[Note: We could not obtain MDS records for 6 NH facilities (ie, 1 veterans home; 2 rehabilitation facilities that were randomized prior to their withdrawal; 1 facility stopped operation in Nov/Dec 2013; still exploring the remaining 2 facilities that did not match]

Outcomes among fee-for-service residents accounting for clustering by NHs

- Hospitalization for respiratory illness RR=.87 P=.02
- All-cause hospitalization RR=.92 P=.003
- Hospitalization for pneumonia RR=.82 P=.04

Abbreviations: CI = confidence interval, FFS = fee-for-service, MDS = minimum data set, RR=relative risk (HD vs. SD homes)

[1] Adjusted for age and average age of facility residents, ADL and average ADL of facility residents, cognitive function, facility hospitalization in prior year and patient chronic heart failure as reported in the MDS. One facility had missing facility covariates, so was excluded from all adjusted analyses.

Gravenstein S, et al. *Lancet: Respiratory Medicine.* 2017.

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Design & Data Issues

- Even with 400+ facilities per arm, lots of heterogeneity by race, baseline hospital use and regional variation in when flu attacks
- Exclusion of Medicare Advantage patients increasing problem in study design; not just waiting for data but facility and regional imbalance from Medicare Advantage concentration
- Time to event outcome ignores multiple events
- Competing Risk of Mortality may underestimate effect since outcome requires hospital admission

Extra slides

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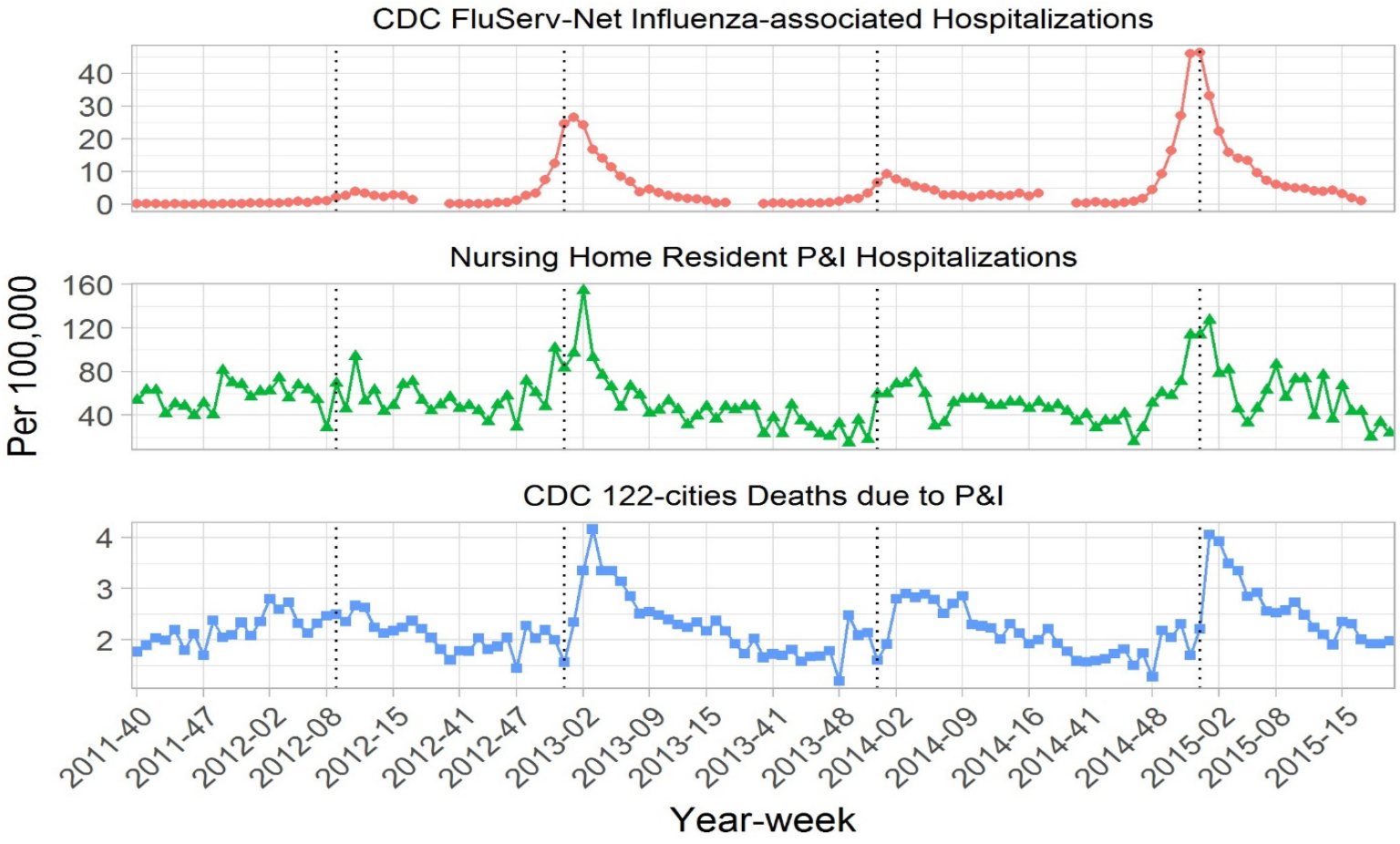
Weekly nursing home hospitalizations from 2011-2015, nursing home residents versus publicly reported measures.



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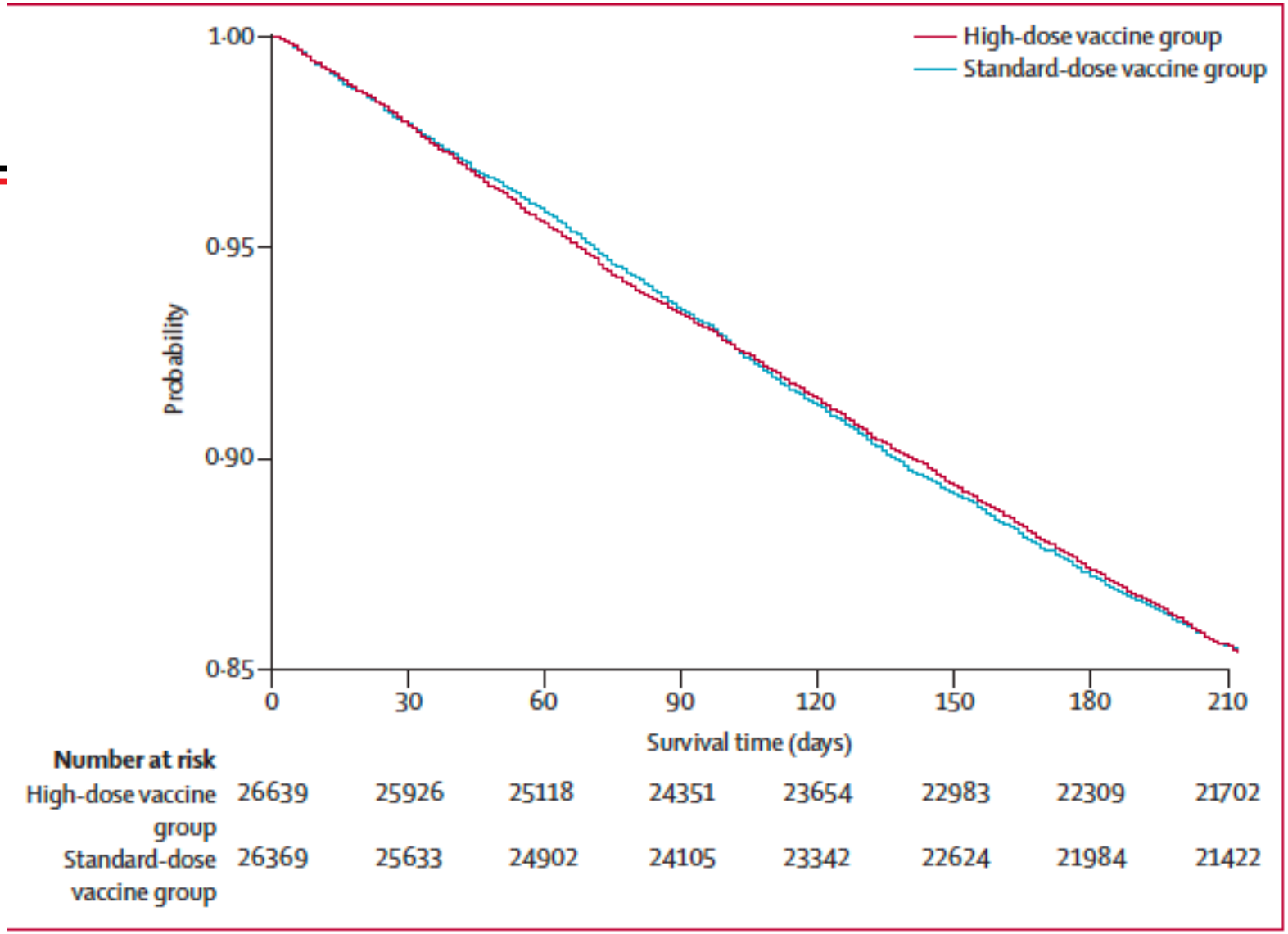

Number at risk								
High-dose vaccine group	26639	25926	25118	24351	23654	22983	22309	21702
Standard-dose vaccine group	26369	25633	24902	24105	23342	22624	21984	21422

Figure 2: **Time to death during the influenza season in residents assigned to either high-dose or standard-dose influenza vaccine for the season 2013–14**

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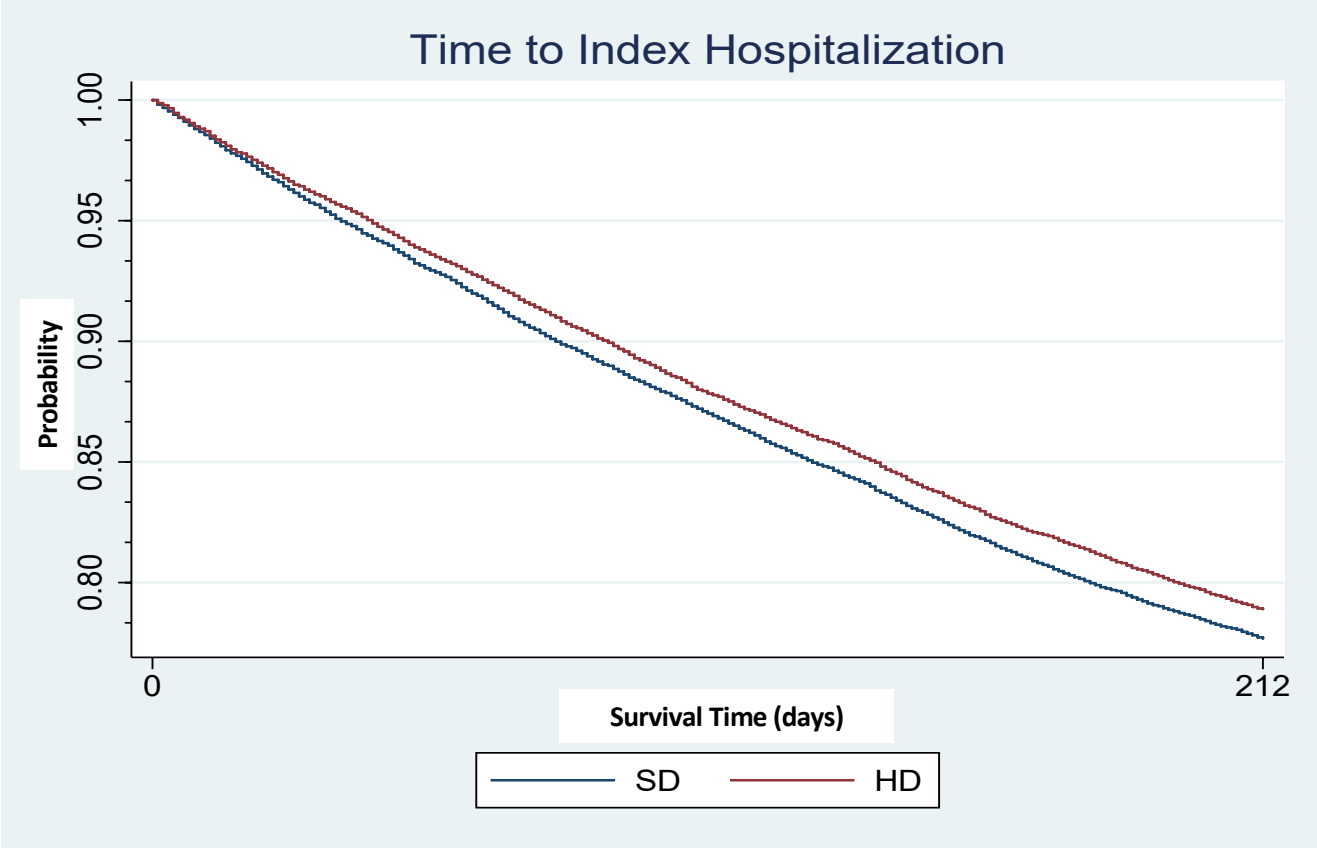
Time to First Respiratory Hospitalization



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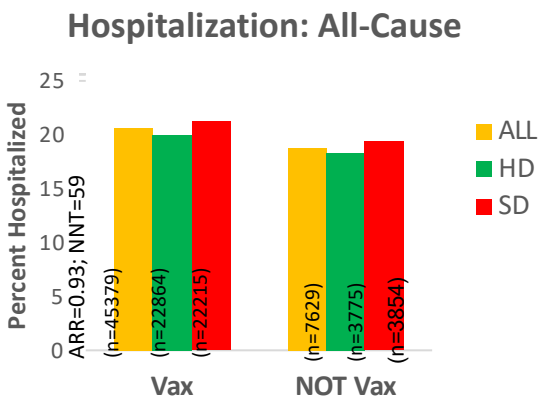
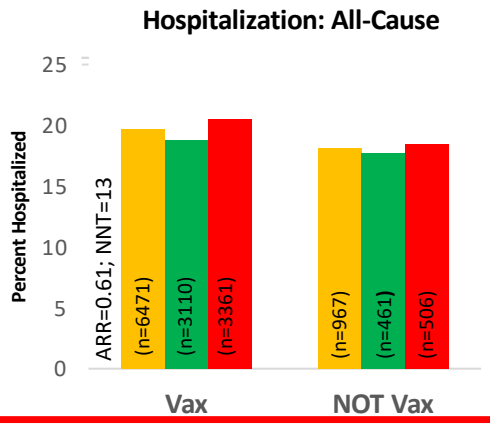
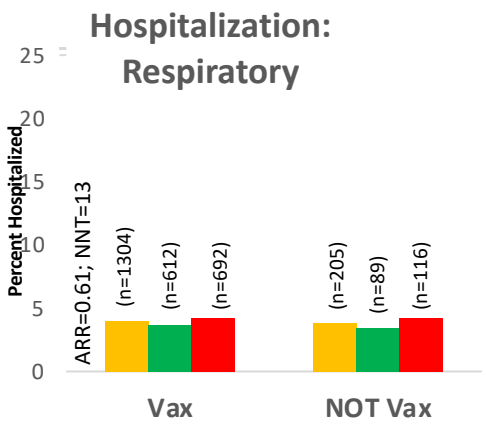
Unvaccinated vs Vaccinated (Unadjusted)
Less Mortality in Vaccinated

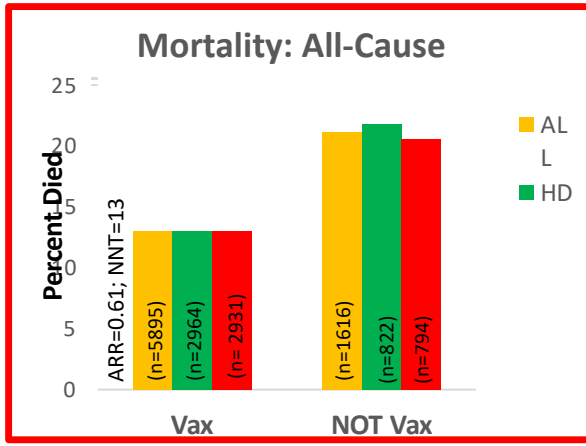
MDS SAMPLE (n=53,008)

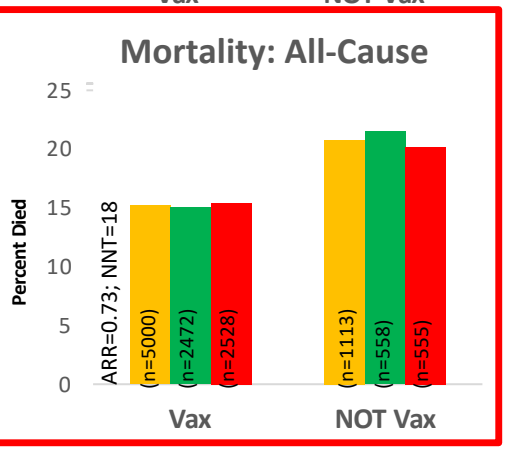


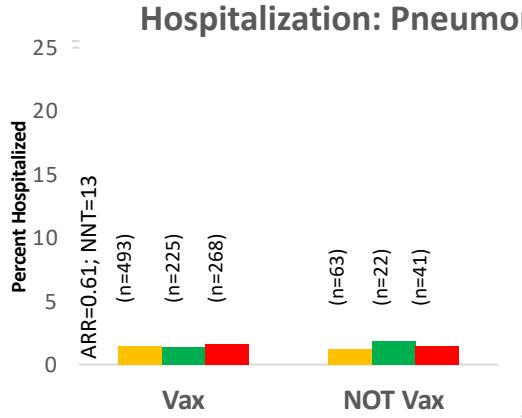
FFS SAMPLE (n=38,256)











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Stakeholder Engagement for Pragmatic Trials Embedded in Clinical Care

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University of Pennsylvania

AcademyHealth Annual Research Meeting
June 3, 2019

Who Are the Stakeholders?

- Who are the stakeholders for explanatory trials?
  - Sponsor / funder
  - Investigators
  - Regulatory agencies
  - Patients
- Who are the stakeholders for pragmatic trials?
  - Health system leaders
  - On-the-ground clinicians
  - Patients

What Do Stakeholders for Embedded PCTs Want?

- Health System Leaders want:
  - interventions that add value
  - quick answers
  - no impact on competing initiatives
- Clinicians want:
  - minimal effect on work-flow
  - answers to questions that are important to them
- Patients want:
  - trials that address outcomes that are important to them

When to Engage Stakeholders

- Early and often
  - Development of trial question
  - Generating grant / funding application
  - During planning and pilot activities
  - Throughout trial conduct
- Building relationships is critical but does not happen quickly

Implications for PCTs: Adherence

- Is adherence relevant?
  - Level of non-adherence should reflect treatment use in everyday practice

    VERSUS
  - Extensive non-adherence will render the data on treatment effects uninterpretable
- How to build in adherence monitoring in design?
- What to do with non-adherence discovered in mid-course?

PROVEN: Adherence

- A Video Status Report User-Defined Assessment (VSR UDA) was programmed in the electronic health record
- Each time a video is offered to a patient or his/her family, a VSR UDA is to be completed – even if a video is not shown.
- VSR UDA linked with MDS data
- Intended to as a measure of adherence for research team and feedback to NHs
- 6 months into implementation
  - Offer rate is low
  - Show rate was low even when offered
  - Particularly bad for long-stay versus admissions

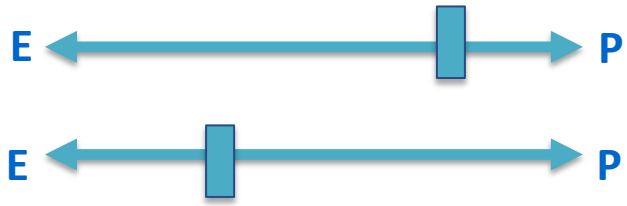
Rule of Thirds for QI Work

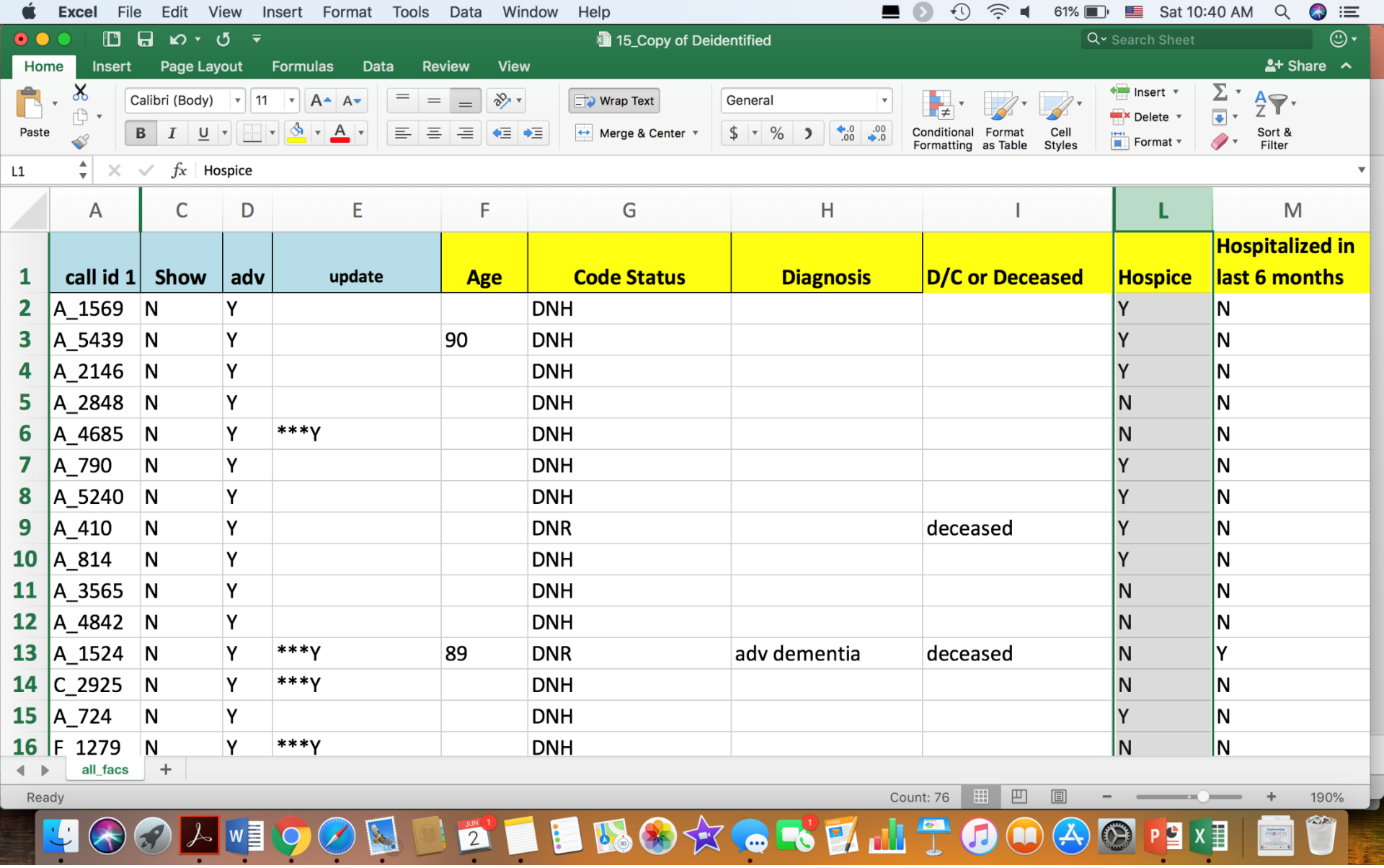
- 1/3 high-performers
- 1/3 somewhat engaged
- 1/3 not engaged

PROVEN: Adherence mid-course corrections

1. Monthly 1:1 calls with ACP Champions in every facility
    - Used MDS to generate a list of long-stay residents who had not been offered a video, i.e., No VSR UDA
        - Champions did not like VSR UDA
        - VSR UDA had about 10% under-estimation of compliance
    - Problem-solved how to reach each individual,
    - Marked increase in offer/show rate
2. Increased enrollment period
3. Proposed 'as treated' secondary analysis

Flexibility: Adherence





	A	C	D	E	F	G	H	I	L	M
1	call id 1	Show	adv	update	Age	Code Status	Diagnosis	D/C or Deceased	Hospice	Hospitalized in last 6 months
2	A_1569	N	Y			DNH			Y	N
3	A_5439	N	Y		90	DNH			Y	N
4	A_2146	N	Y			DNH			Y	N
5	A_2848	N	Y			DNH			N	N
6	A_4685	N	Y	***Y		DNH			N	N
7	A_790	N	Y			DNH			Y	N
8	A_5240	N	Y			DNH			Y	N
9	A_410	N	Y			DNR		deceased	Y	N
10	A_814	N	Y			DNH			Y	N
11	A_3565	N	Y			DNH			N	N
12	A_4842	N	Y			DNH			N	N
13	A_1524	N	Y	***Y	89	DNR	adv dementia	deceased	N	Y
14	C_2925	N	Y	***Y		DNH			N	N
15	A_724	N	Y			DNH			Y	N
16	F_1279	N	Y	***Y		DNH			N	N

Implications for PCTs: How to monitor

- Adherence monitoring
  - Tension between introducing “new” measure of adherence and being “pragmatic”
  - Front-line providers (who don’t know this is “research”) may not comply with “new forms” if they don’t see clinical relevance

Implications for PCTs: What to do

- Consequences of non-adherence
  - Intention-to-treat analyses
  - "Implementation" error
  - Concern for DSMB
- Strategies for dealing with non-adherence
  - Careful planning
  - Mid-course correction
  - Per-Protocol Analysis