

# The Diuretic Comparison Project : Practical Issues with a Pragmatic Trial

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# Chlorthalidone Versus Hydrochlorothiazide: A New Kind of Veterans Affairs Cooperative Study

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*Ann Intern Med.* 2016;165:663-664.

## Investigators:

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# The VA Point of Care Program

- Goal: large inexpensive RCTs
- Optimize use of EMRs
- Avoid the cost of “the clinical trial apparatus”
- Recruitment/randomization “at the point of care”
- DCP is the first full scale RCT in this program

# Diuretic Comparison Project

## Study Question

Does treatment with chlorthalidone (CTD) reduce major adverse cardiovascular events (MACE) compared with hydrochlorothiazide (HCTZ) in older veterans with hypertension?

# CTD has done well in RCTs

- No 'CTD vs HCTZ' RCTs for clinical outcomes
- Network meta-analysis
  - 21%↓ in MACE for CTD vs. HCTZ;
  - 18% ↓ when adjusted for attained BP  
(Roush, HTN 2012;59:1110-7)
- NIH trials used CTD, most other trials used HCTZ
  - Is it the CTD or the NIH?

# CTD vs. HCTZ – what's the difference?

- Studies show CTD has  $\approx 2x$  the potency of HCTZ
- But CTD not used at lower doses (? savvy CTD users)
- CTD has longer elim. half-life (50-60 hrs vs 9-10 hrs)
- CTD has longer elim. half-life (con't)
- One *in vitro* study of pleiotropic effects:  
CTD  $\rightarrow$   $\downarrow$  plt aggregation &  $\uparrow$  angiogenesis vs. a thiazide

# Why not just switch everyone over?

Besides the usual risks of centralized decision-making, it costs more:

## VA Costs

- HCTZ 50 mg = 1.6¢
- CTD 25mg = 11¢
- 7-fold increase = \$18 million/year more for 1 million VA patients

Plus, not everyone agrees ...

# Chlorthalidone Versus Hydrochlorothiazide for the Treatment of Hypertension in Older Adults

| 19 March 2013 | Annals of Internal Medicine | Volume 158 • Number 6

## A Population-Based Cohort Study

Irfan A. Dhalla, MD, MSc; Tara Gomes, MHSc; Zhan Yao, MD, MS; Jeff Nagge, PharmD; Navindra Persaud, MD, MSc; Chelsea Hellings, MSc; Muhammad M. Mamdani, PharmD, MA, MPH; and David N. Juurlink, MD, PhD

**Conclusion:** As typically prescribed, chlorthalidone in older adults was not associated with fewer adverse cardiovascular events or deaths than hydrochlorothiazide. However, it was associated with a greater incidence of electrolyte abnormalities, particularly hypokalemia.



# DCP Study Design

- Prospective randomized open-label blinded-endpoint (PROBE) trial.
- Centralized informatics-based clinically integrated structure.
  - Embedded within EMR or backend database.
  - Clinical workflows used to facilitate training.
- N=13500
- HCTZ users randomized to stay on current therapy or to initiate CTD

# Inclusion/Exclusion Criteria

## Inclusion:

1. Over age 65 years (half outcomes outside VA)
2. On HCTZ 25 or 50 mg/d from VA (not combo)
3. Most recent SBP (in CPRS)  $\geq 120$  mm Hg, & no SBP  $< 120$  mm Hg w/in 90 days before randomization (minimize risk, maximize benefit)

## Exclusion:

1. Considered incompetent to consent
2. Death expected within 6 months
3. Na  $< 130$  meq/L or K  $< 3.1$  meq/L in past 90 days (enroll them later)
4. Known to be in Medicare Part C  
(HMO pts, no outcome data)

# Study Intervention

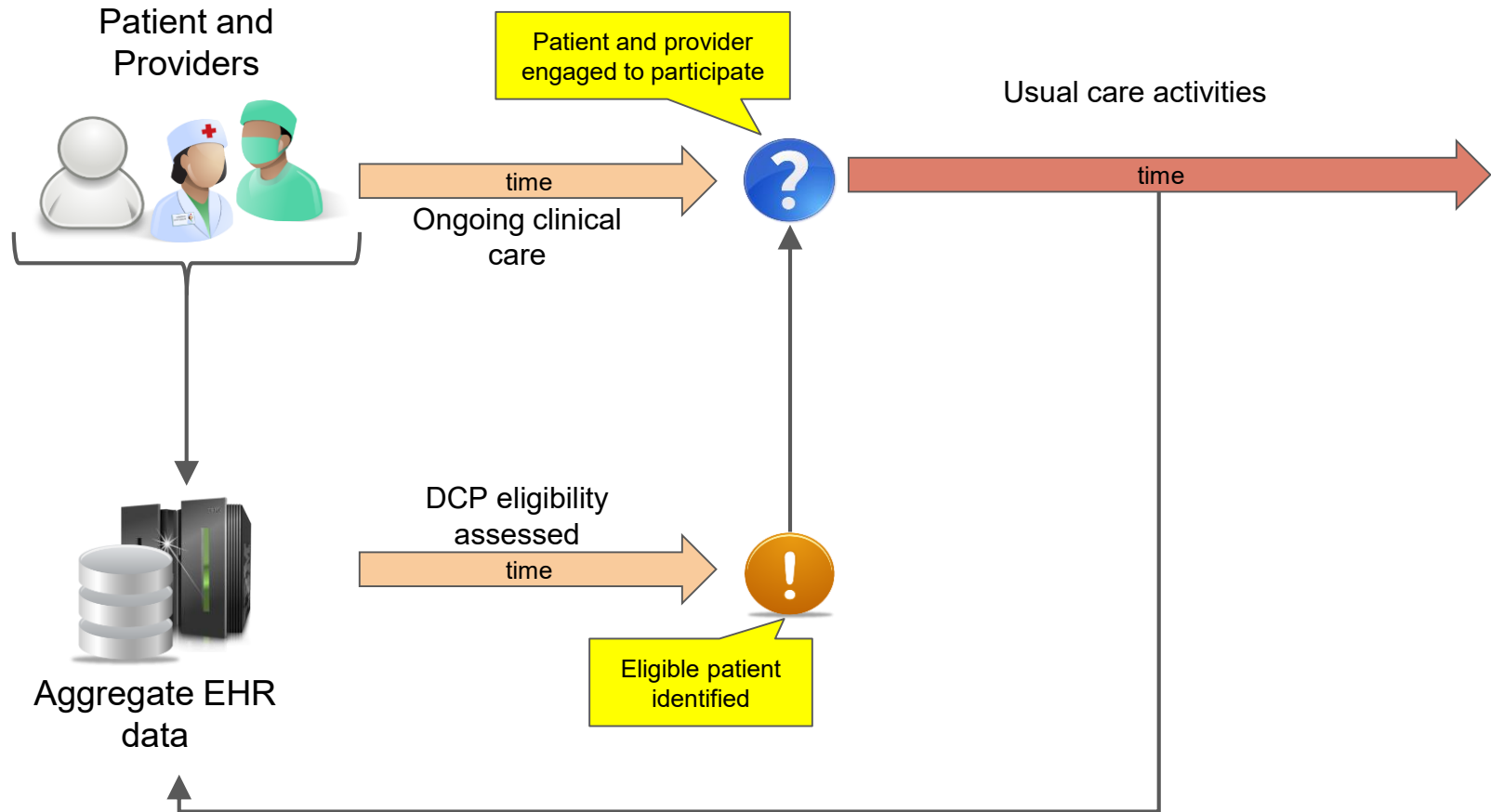
- Drug is open-label but allocation is concealed
- Randomize to current dose HCTZ (25 or 50 mg), or half that dose of CTD (12.5 or 25 mg)
- Change to CTD → order to PCP
  - For 12.5 mg, send tablet splitter with rx
  - Re-imburse pt for co-pay of discarded HCTZ
- All mgmt by PCP (lab, drug, dose)

# The primary outcome - MACE

Time to first occurrence of any of the following:

1. Stroke
2. Myocardial infarction
3. Urgent coronary revasc 2° unstable angina
4. Hospitalization for acute decompensated HF
5. Non-cancer death

# Simplified DCP Workflow



# Pragmatic Features:

- 1) Design with technology as a force multiplier
- 2) Embedded within VA Information Systems & EMR
  - find eligible patients using VA EMR
  - centralized recruitment and enrollment
  - centralized placement of notes & orders
  - PCPs: permission & pt care (including study drug)
  - centralized collection of outcomes from EMR database

# Pragmatic Features:

- 3) Clinical sites not “engaged in research” - no local personnel (10% cost)
- 4) Telephone base informed consent for participants with a clinical assent to maintain clinical autonomy
- 5) Minimal perturbation of the clinical workflow. Study designed to “fold into” PCP processes

# Lessons Learned

- Focus groups for implementation:
  - Providers – clinical autonomy, consent, buy-in.
  - Patients – worry about a lot less than we worry about.
  - Oversight – “engaged” partners; safety reporting and DMC
- Design of projects:
  - Limitations of real world data need to be accounted for and mitigations/controls built into system



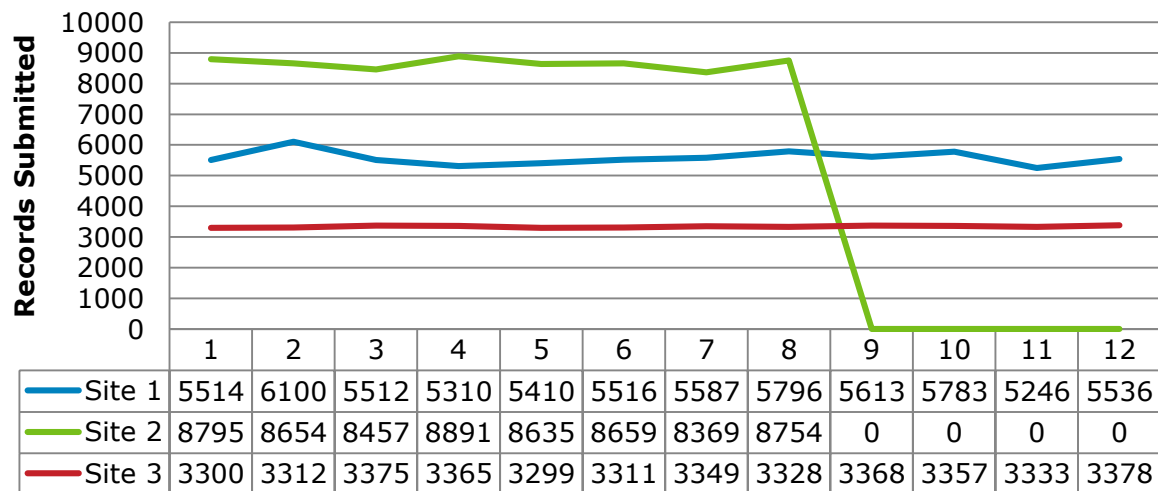
# Lessons Learned

- Data Systems
  - Robust algorithms for ascertainment planned and operationalized prior to launch (upfront informatics work); compromised by data structure.
  - Accuracy and Cleanliness of Data are not perfect – secondary use of medical record reshapes convention
    - Expectations of encounters – (Na, K, etc)
    - ‘Imperfect’ entry; unvalidated data
    - Hospital operations take priority over research and learning.

# Lessons Learned

- Data Systems
  - Sentinel systems are required when merging data sets.

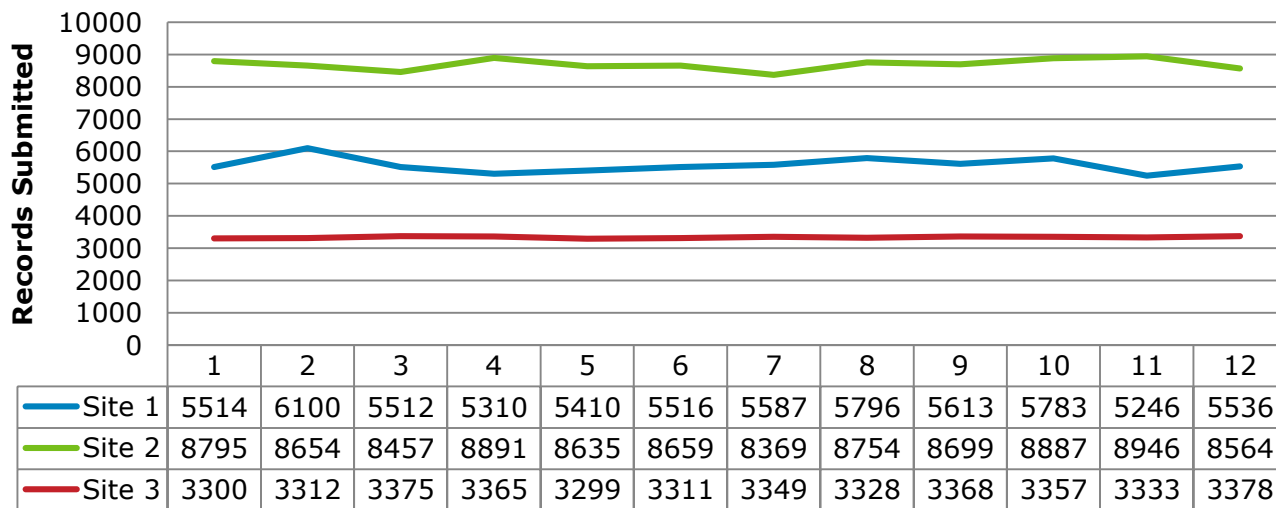
## Data Submission to Database Prior to Sentinel



# Lessons Learned

- Data Systems
  - Sentinel systems are required when merging data sets.

**Data Submission to Database After Sentinel**



# Closing

- Reduction in barriers to participation has a real world impact.
  - Consent rates higher than traditional trials.
  - Assent rates and PCP participation higher than other CSP trials
- Generalizability may be limited beyond the VA System -- “Locally selfish” learning.
- Use of Real World Data is challenging reality for the clinical trials enterprise.

# Supplemental Slides on EMR

# View Alert for Approval to Recruit Patients in PCP's Panel

The screenshot shows a software window titled "Patient Selection" with a close button (X) in the top right corner. The window is divided into two main sections: "Patient List" and "Notifications".

**Patient List Section:**

- Patient List:** Patients (PACT TEAM D3)
- Filters:** A group of radio buttons on the left allows filtering by:
  - Default: PACT TEAM D3
  - Providers
  - Clinics
  - Team/Personal
  - Wards
  - Specialties
  - All
- Patient List:** A scrollable list of patient names:
  - ZzdcP Patient,Actual
  - Zztest,A
  - Zztest,Patent B
  - Zztest,Patent
  - Zztest,Pharmacy X
  - Zztest,Xx
  - Zztest,Zachary
  - Zztest,Zen
  - Zztest,Zinc
- Buttons:** "OK", "Cancel", and "Save Patient List Settings" are located on the right side.

**Notifications Section:**

Info	Patient	Location	Urgency	Alert Date/Time	Message
	ZZTEST_DCP [Z2001]		HIGH	09/12/2013@15:16	Order requires electronic signature.

At the bottom of the window, there is a row of buttons: "Process Info", "Process All", "Process", "Forward", "Show Comments", and "Remove".

# Order to Screen/Recruit Eligible Patients in PCP's Panel

File Edit View Action Options Tools Help

**ZZTEST,RESEARCH USE ONLY MIN Z (OUTPATIENT)** 16194 Jul 18,17 15:48 No PACT assigned at any VA location / VistaWeb ? No Postings  
 000,00-8026 Jan 01,1973 (44) Provider: \_\_\_\_\_ Flag Remote Data

View Orders Unsigned Orders - ALL SERVICES

Service	Order	Start / Stop	Provider	N...	C	Chart	Status	Location
Other	<p>&gt;&gt; Approve sending information/opt-out letters from DR. PCP NAME to eligible patients in this provider's panel. for the VA Diuretic Comparison Project.</p> <p>&gt;SIGN this order to ACCEPT mailing information/opt-out letters to eligible patients in this provider's panel.            &gt;Also read ***Research PROGRESS NOTE*** on this test patient.</p> <p>&gt;DISCONTINUE this order to REMOVE this provider's panel from this project.            &gt;For more information go to <a href="http://www.research.va.gov/programs/csp/597">www.research.va.gov/programs/csp/597</a>.            *UNSIGNED*</p>	Start: Now Stop: Today+30	Lederle,				unreleas	Msp Adr

Write Delayed

Write Orders

Menus/Set

Psych Inpt  
 CLC Inpt O  
 SCI/D Inpt  
 Surgery Inp  
 Medicine Ir  
 TeleICU Inj

=====  
 Medicine O  
 Surgery Ou  
 Mental Hea  
 EC&R Outp  
 SCI/D Outp  
 Emergency  
 CBOC Orde  
 Twin Ports

Generic

Enter Allerg  
 Outpatient  
 Diet Order()  
 npatient M

“right click” order

- Details...
- Results...
- Results History...
- Change...
- Change Release Event
- Copy to New Order...
- Discontinue...
- Renew...
- Sign...

# After patient consents: PCP approval to randomize

Vista CPRS in use

File Edit View Action Options Tools Help

DCP, ELIGIBLE PATIENT (OUTPATIENT) RESEARCH Jan 26, 16 08:35 PACT TEAM B-1/ Provider, Other Md  
000-00-9234 Oct 29, 1949 (66) Provider: PROVIDER, OTHER

View Orders Active Orders (includes Pending & Recent Activity) - ALL SERVICES

Service	Order	Start / Stop	Provider
Other	>> Approve randomization of this patient to the Diuretic Comparison Project to receive HCTZ or chlorthalidone. >SIGN this order to ACCEPT this patient as appropriate for randomization. >DISCONTINUE this order to REMOVE this patient from the project. For more information see Research PROGRESS NOTE. *UNSIGNED*	Start: Now Stop: Today+770	Provider, Other

Write Delayed Orders

Write Orders

- Details...
- Results...
- Results History...
- Change...
- Change Release Event
- Copy to New Order...
- Discontinue...
- Renew...
- Sign...

Cover Sheet Problems Meds Orders Notes Consults Surgery D/C Summ Labs Reports



The patient is then randomized  
by Boston MAVERIC CSPCC  
(and is 'in' the study - ITT)

# Randomization Orders

[Options](#) [Tools](#) [Help](#)

**TIENT (OUTPATIENT)**

Oct 29, 1949 (66)

**RESEARCH Jan 26, 16 08:35**

Provider: PROVIDER, OTHER

PACT TEAM B-1/ Provider, Other Md

Active Orders (includes Pending & Recent Activity) - ALL SERVICES

CES	Service	Order	St
	Activity	>> VA Diuretic Comparison Project +++++Patient randomized to Chlorthalidone+++++ 1. Continue to manage per usual care. 2. See Research PROGRESS NOTE for information. 3. Please Accept/Bypass the DUPLICATE THERAPY warning. Thank you for participating in this important project. *UNSIGNED*	St St
	Out. Meds	CHLORTHALIDONE TAB 25MG TAKE ONE-HALF TABLET BY MOUTH EVERY DAY Quantity: 45 Refills: 3 *UNSIGNED*	St
		TABLET SPLITTER MISCELLANEOUS TABLET CUTTER USE ITEM AS DIRECTED BY PROVIDER ONCE Use to split pills in half. Quantity: 1 Refills: 0 *UNSIGNED*	St
		Discontinue HYDROCHLOROTHIAZIDE TAB 25MG TAKE ONE TABLET BY MOUTH EVERY MORNING FOR BLOOD PRESSURE Quantity: 90 Refills: 0 *UNSIGNED* <Requesting Physician Cancelled>	

# “Please accept/bypass the Duplicate Therapy warning”

## Order Checks

To cancel an order select the order by checking the checkbox and press the "Cancel Checked Order(s)" button.

If the order check description is cut short, hover over the text to view the complete description.

Cancel	Order/Order Check Text
<input type="checkbox"/>	CHLORTHALIDONE TAB 25MG TAKE ONE-HALF TABLET BY MOUTH EVERY DAY Quantity: 45 Refills: 3 *UNSIGNED*
	(1 of 1) Duplicate Therapy: Order(s) exist for {HYDROCHLOROTHIAZIDE 25MG TAB [SUSPENDED]} in the same therapeutic categor(ies): Thiazide and Related Diuretics

Cancel Checked Order(s)

Accept Order(s)

Return to Orders

Drug Interaction Monograph

# Randomization Note

File Edit View Action Options Tools Help



**ZZTEST,RESEARCH USE ONLY MIN F (OUTPATIENT)**

000-00-8006

Jan 01,1953 (64)

**16194 Jul 18,17 14:50**

Provider:

No PACT assigned at any VA location /

Flag

VistaWeb

Remote Data



No Postings

Last 100 Signed Notes

- ▲ New Note in Progress
  - ☐ Jul 18,17 RESEARCH/DIURETIC COMPARISON PROJECT
- ▲ All signed notes
  - ☐ May 11,17 RESEARCH/DIURETIC COMPARISON PROJECT
  - ☐ Apr 26,17 RESEARCH/DIURETIC COMPARISON PROJECT
  - ☐ Apr 25,17 RESEARCH/DIURETIC COMPARISON PROJECT
  - ☐ Apr 24,17 RESEARCH/DIURETIC COMPARISON PROJECT
  - ☐ Apr 21,17 RESEARCH/DIURETIC COMPARISON PROJECT
  - ☐ Feb 21,17 RESEARCH/DIURETIC COMPARISON PROJECT

RESEARCH/DIURETIC COMPARISON PROJECT

Vst: 07/18/17 MSP ADMINISTRATIVE CLINIC-X Jul 18,2017@15:03

Change...

DOCUMENTATION FOR DIURETIC COMPARISON PROJECT

This patient has consented to participate in the VA Point of Care Diuretic Comparison Project comparing the effectiveness of chlorthalidone and hydrochlorothiazide (HCTZ) in reducing cardiovascular events in the treatment of hypertension. Follow-up will be collected passively.

1. This patient has been randomized to Chlorthalidone.
2. The Primary Care Provider (PCP) should treat the patient according to usual care.
3. NEW ORDERS awaiting concurrence and signature of PCP:
  - a. Text order denoting randomization to Chlorthalidone.
  - b. Discontinuation of the current HCTZ and
  - c. Chlorthalidone 12.5mg daily.

The PCP may accept the orders as ordered, change the dose or discontinue the new orders.

The PCP may also wish to order any desired laboratory tests or blood pressure checks.



Active **B**athing to **E**liminate Infection Project

**NIH Collaboratory Workshop**  
**May 19, 2018**

Susan Huang, MD MPH  
Professor and Hospital Epidemiologist  
University of California Irvine School of Medicine  
for the ABATE Infection Trial Team

# Healthcare-Associated Infections (HAIs) in the United States

- 1.7 million hospital-associated infections
  - 4.5 per 100 admissions
- 99,000 deaths associated with HAI infections
  - 36,000 pneumonias
  - 31,000 bloodstream infections

# ICU Efforts to Reduce HAIs

- Efforts focused on high-risk ICUs
  - Body bacteria often cause infection in ICUs
  - Decolonization to reduce body bacteria
- REDUCE MRSA Trial
  - Conducted in Hospital Corporation of America system
  - 43-hospital cluster randomized trial of ICU decolonization
  - Daily chlorhexidine (CHG) baths plus nasal mupirocin
  - Reduced MRSA clinical cultures by 37%
  - Reduced ICU bloodstream infections by 44%

# What About Outside the ICU?

- >75% of hospital-associated infections are outside ICUs
- 2010-2016
  - ICU reductions >> non-ICU reductions
  - Would decolonization be useful?



# ABATE Infection Trial

## Active Bathing to Eliminate Infection

### Trial Design

- 2-arm cluster randomized trial
- Adult non-critical care hospital units
- Includes: adult medical, surgical, step down, oncology
- Excludes: rehab, psych, peri-partum, BMT

### Arm 1: Routine Care

- Routine policy for showering/bathing

### Arm 2: Decolonization

- Daily CHG shower or CHG cloth bathing for all patients
- Mupirocin for 5 days if MRSA+ by history, culture, or screen

# ABATE Infection Trial

## Outcomes

### Primary Outcome

- **Unit-attributable clinical cultures with MRSA and VRE\***

### Secondary Outcomes

- **All-cause bloodstream infections\***
- Unit-attributable clinical cultures with GNR MDRO
- Bloodstream contaminants
- Urinary tract infections: all pathogens
- *Clostridium difficile* infections
- 30 day readmissions (total and infectious)
- Emergence of resistance (strain collection)

\* Primary manuscript

# ABATE Infection Trial

## Timeline and Participants

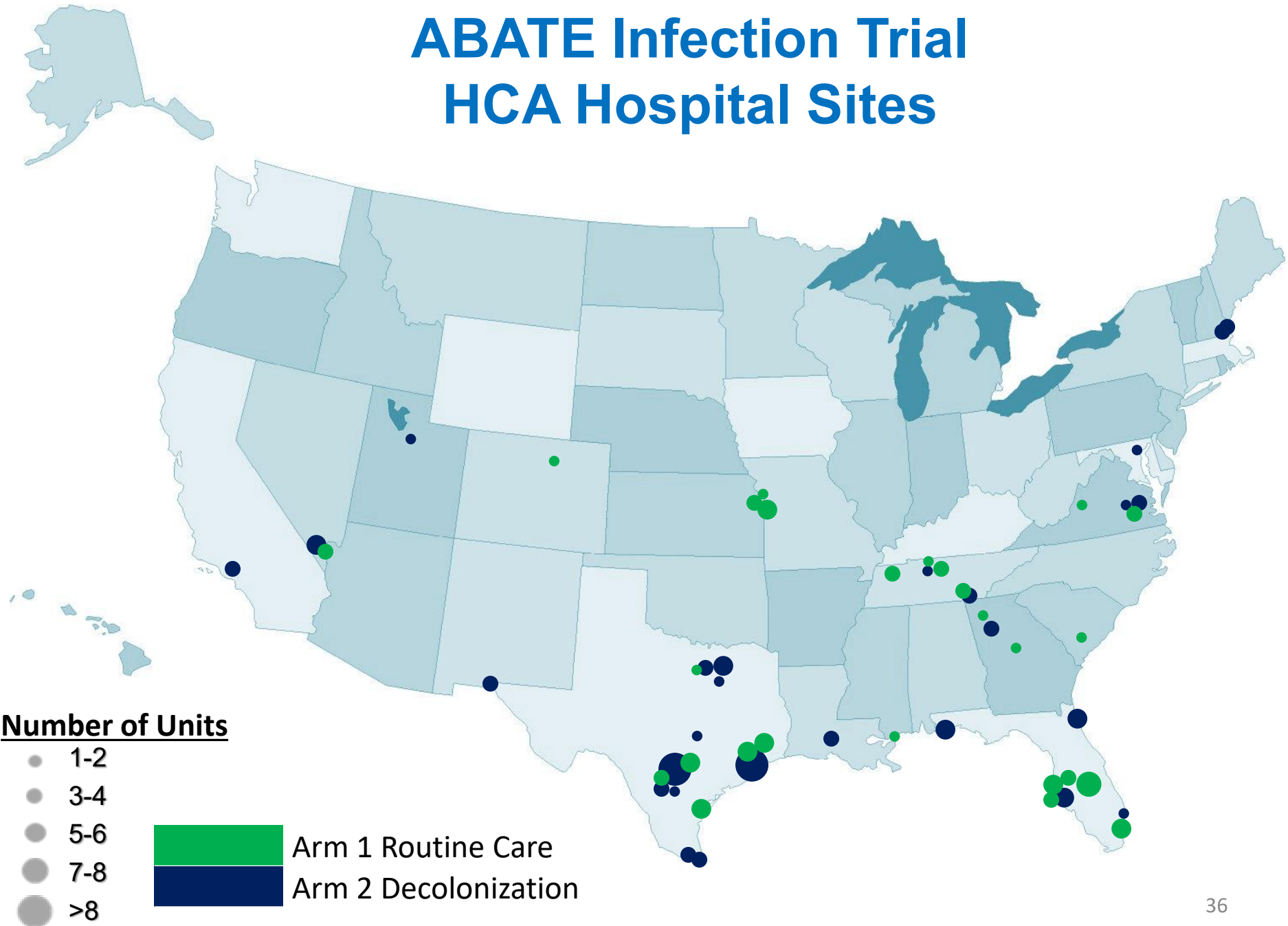
### Timeline

- Baseline (12-months)      March 2013-Feb 2014
- Phase-In (2-months)      April 2014-May 2014
- Intervention (21-months) June 2014-Feb 2016

### Participants

- 53 HCA hospitals
- 194 adult non critical care units
- Total patients: 528,983
  - Baseline period: 244,166
  - Intervention period: 284,817

# ABATE Infection Trial HCA Hospital Sites



# Pragmatic Activities

## Successes

- Centralized recruitment and IRB
- Compliance and feedback
- Use of routine centralized medical record data

## Complexities

- Chlorhexidine compatibility
- Competing interventions
- Tracking adverse events

# Pragmatic Activities

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## Complexities

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# Corporate Support: Recruitment and IRB

## Recruitment

- 53 hospitals in under 3 months
- Corporate communication channels
- Recruitment invitation flyers, pitch on standing CMO/CNO calls
- Internal leaders reached out to contacts

## IRB

- Harvard centralized IRB approval, waiver informed consent
- Ceding completed in 5 months: FWA, human subjects training
- Corporate compliance support
- Prisoner review

# Pragmatic Activities

## Successes

- Centralized recruitment and IRB
- **Compliance and feedback**
- Use of routine centralized medical record data

## Complexities

- Chlorhexidine compatibility
- Competing interventions
- Tracking adverse events



# Computer Based Training

- Web based training module with audio for each study arm
  - **Arm 1 module:** 11 slides + 6 question post-test
  - **Arm 2 module:** 30 slides + 8 question post-test
- Required for all nursing staff on participating units
- Continued use for training new staff
- Number of annual CBTs completed

	2014	2015
Arm 1	3,407	2,022
Arm 2	4,928	3,721
<b>Total</b>	<b>8,335</b>	<b>5,743</b>

# Electronic Compliance Tracking Corporate ABATE Nursing Query

ABATE Infection Study

01/30 1349 SMS J00009190860 SCOTT,SCOTT

**Bath in 24 hours**

- 1 No bath
- 2 Bath/Shower with CHG includes pre-surgical bathing
- 3 Bath/Shower without CHG

Hygiene Care

Bath/Shower in past 24 hours:

Reason for no bath:

Query Documentations: **1.6 million across both arms**

# Tableau Reports

- Corporate IT&S developed user friendly reports to capture bathing and mupirocin administration
- Eased process for completing compliance spreadsheets

Workbook: ABATE\_CHG in Project: ABATE

Name	Sheet #	Owner	Modified
Compliance Percentage	1	Forehand Tyler	Today, 7:04 AM
Compliance Detail	2	Forehand Tyler	Today, 7:04 AM
CHG Utilization Detail	3	Forehand Tyler	Today, 7:04 AM

Rows per page: 50 Pages: 1 / 1

ABATE\_CHG Back Workbook

Compliance Percentage Compliance Detail CHG Utilization Detail

**Documentation Compliance Detail**  
# of documentations / # of Patients  
\*1 documentation per patient max

Last Updated 1/15/2015 7:04:11 AM

Compliance Breakdown

	11/1/2014	11/2/2014	11/3/2014	11/4/2014	11/5/2014	11/6/2014
# of Patients	11	6	13	4	9	13
Admit Day(Partial)	6	2	7	1	3	9
Intra Day(Full)	16	21	17	10	14	15
Discharge Day(Partial)	7	6	6	10	6	8
# of Pats w/ at least 1 Documentation	6	2	7	11	3	9
Admit Day(Partial)	4	2	7	1	3	9
Intra Day(Full)	13	17	12	12	14	9
Discharge Day(Partial)	1	0	2	3	5	2
<b>Grand Total</b>	<b>34</b>	<b>33</b>	<b>38</b>	<b>32</b>	<b>31</b>	<b>36</b>
# of Pats w/ at least 1 ..	22	19	21	16	22	18

Built by HCA  
Corporate IT&S Team

Filter by "Location" (unit)

**Arm 2 Compliance Form**

Bathing Documentation on Assessment Day

Total # of Patients in Unit	# Patients with Completed Bathing Prompt	Missed Opportunity	Documentation Compliance
24	12	12	50%
34	22	0	65%
		0	#DIV/0!
		0	#DIV/0!

# Arm 2 – Quarterly Staff and Patient Compliance Assessments

Hospital Name: \_\_\_\_\_ Unit Name: \_\_\_\_\_

**HCA** Skills Assessment:  
Hospital Corporation of America™ **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**

- How many cloths were used (1 cloth set = 6 cloths, 1 cloth set plus 1 single pack = 8 cloths)  
\_\_\_\_\_
- If more than 1 cloth set (6 cloths) was used, provide reason.  
\_\_\_\_\_
- Do you reapply CHG after an episode of incontinence has been cleaned up?  
\_\_\_\_\_
- Are you comfortable applying CHG to superficial wounds, including surgical wounds?  
\_\_\_\_\_
- Are you comfortable applying CHG to lines, tubes, drains and non-gauze dressings?  
\_\_\_\_\_
- Do you ever wipe off the CHG after bathing?  
\_\_\_\_\_

Email to [ABATEStudy@gmail.com](mailto:ABATEStudy@gmail.com) or fax to (949) 824-3985

# completed: 1,469

Hospital Name: \_\_\_\_\_ Unit Name: \_\_\_\_\_


**HCA** Skills Assessment:  
Hospital Corporation of America™ **CHG Cloth – Patient Self-Bathing**

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

**CHG Showering – Patient Self-Bathing**

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

**Questions**

- Were you provided a handout with instructions on how to apply the CHG liquid in the shower?  
 Y     N
- Were you told that CHG kills germs better than regular soap and water?  
 Y     N
- Did you use the mesh sponge to apply the CHG?   Y     N
- Did you soap up twice with CHG before rinsing?  
 Y     N
- Did you leave the CHG on your skin for 2 minutes before rinsing off?  
 Y     N
- Were you told NOT to use other bathing soaps or lotions while in this unit?  
 Y     N
- Were you told to bathe or shower daily with CHG while in this unit?  
 Y     N
- Did you or an assistant clean your lines, tubes, and/or drains with a CHG cloth after showering?  
 Y     N     N/A
- Did you or an assistant clean your wounds with a CHG cloth after showering?  
 Y     N     N/A

# completed: 1,251

# Pragmatic Activities

## Successes

- Centralized recruitment and IRB
- Compliance and feedback
- **Use of routine centralized medical record data**

## Complexities

- Chlorhexidine compatibility
- Competing interventions
- Tracking adverse events

# Types of Data

## Admission

Hospital ID  
Admission ID  
Encrypted Patient ID  
Admission Dates  
Sex  
Ethnicity  
Insurance  
21 Diagnoses codes  
21 POA indicators  
15 Procedure codes  
Final disposition

## Nursing Query

Hospital ID  
Admission ID  
Encrypted Patient ID  
Specimen ID  
Nursing Date  
Unit / Charge Type  
Chlorhexidine bath

## Supply Chain

Unit Level  
Gloves, gowns, alc rub

## Charge

Hospital ID  
Admission ID  
Charge Date  
Unit / Charge Type  
Unit name  
Mupirocin use  
Chlorhexidine use

## Lab

Hospital ID  
Admission ID  
Encrypted Patient ID  
Specimen ID  
Collection Date  
Screen vs. Culture  
Pathogen  
Antibiotic  
Result

Total Admissions: >500,000  
Total Patient Days: 2+ million

# Pragmatic Activities

## Successes

- Centralized recruitment and IRB
- Compliance and feedback
- Use of routine centralized medical record data

## Complexities

- **Chlorhexidine compatibility**
- Competing interventions
- Tracking adverse events

# Ensuring CHG Compatibility

- Several lotions, ointments, incontinence cleanup and barrier products, soap and bathing products inactivate CHG
- Intervention units
  - ~200 products reviewed
  - Removed incompatible skin products
  - Manufacturers contacted for compatibility
  - Alternative options provided



# Pragmatic Activities

## Successes

- Centralized recruitment and IRB
- Compliance and feedback
- Use of routine centralized medical record data

## Complexities

- Chlorhexidine compatibility
- **Competing interventions**
- Tracking adverse events

# Intervention Tracking

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

Arm	Proposed Interventions	Allowed	Not Allowed (Conflicting)
1	83	47 (57%)	36 (43%)
2	102	73 (72%)	29 (26%)
Division	9	7 (78%)	2 (22%)
Corporate	2	2 (100%)	0 (0%)
<b>Total</b>	<b>196</b>	<b>129 (66%)</b>	<b>67 (34%)</b>

**3 sites withdrew from trial due to conflicting intervention**

# Pragmatic Activities

## Successes

- Centralized recruitment and IRB
- Compliance and feedback
- Use of routine centralized medical record data

## Complexities

- Chlorhexidine compatibility
- Competing interventions
- **Tracking adverse events**

# Safety of Decolonization

## Study-related events

- Monthly reminders to report
- 1.1 million estimated bathing days
- Mupirocin: no study related events
- CHG events: 25 (all mild)

## Challenges of tracking

- Nurses comfortable with product → less reporting
- Mild rash not uncommon in hospital → not reported
- Events likely underestimated

# Summary: ABATE Infection Trial

## Pragmatism

- Corporate partnership, engagement made the trial possible
- Provided communication, endorsement, expectations
- Enabled standardized data and reporting
- Resolved complexity: supply chain for compatibility
- Provided insight to extent of competing interventions
- Limits adverse event tracking

# Special Thanks: ABATE Team



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Active **B**athing to **E**liminate Infection Project

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# COMBINE

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Anti-TNF Monotherapy versus Combination  
Therapy with Low Dose Methotrexate in Pediatric  
Crohn's Disease

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May 16, 2018



# Background

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## Crohn's disease

- ▶ Chronic gastrointestinal inflammatory condition
- ▶ Substantial patient burden
  - GI symptoms (abdominal pain, diarrhea, bleeding)
  - Fatigue, anxiety, and depression
  - Functional impairments/quality of life
  - Growth, pubertal development (in children)
- ▶ Public Health Burden
  - 1.4 million Americans with IBD
    - 50,000-75,000 children
  - > \$6 billion in direct costs

# High Stakes Treatment Decisions

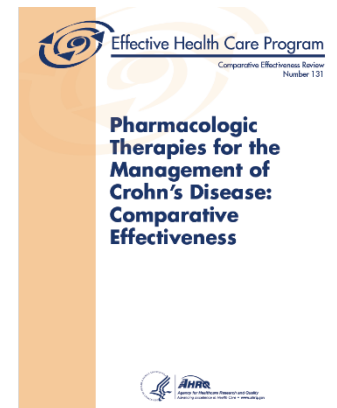
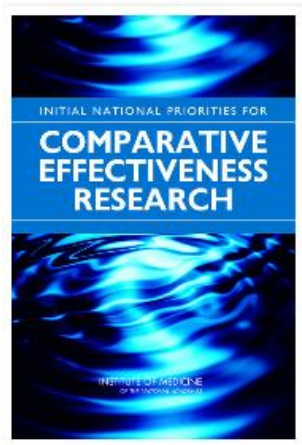
## ▶ Balancing substantial benefits and risks

Benefits	Risks
Symptom improvement	Immune suppression
Restoration of normal growth and development	Organ toxicity (liver, kidney, bone marrow)
Prevention of complications of disease <ul style="list-style-type: none"><li>• Abscess</li><li>• Stricture</li><li>• Need for surgery</li><li>• GI malignancy</li></ul>	Cancer (lymphoma, skin)

## ▶ Treatment is costly (~\$50-100K per year)

# Need for CER

- ▶ 2009 Institute of Medicine CER report: top quartile research priority
- ▶ 2014 AHRQ report: "Comparing Crohn's disease medications directly using pragmatic clinical trials will help to understand the effectiveness of medications in clinical practice"



# #1 Research Priority

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## **Anti-TNF combination vs monotherapy**

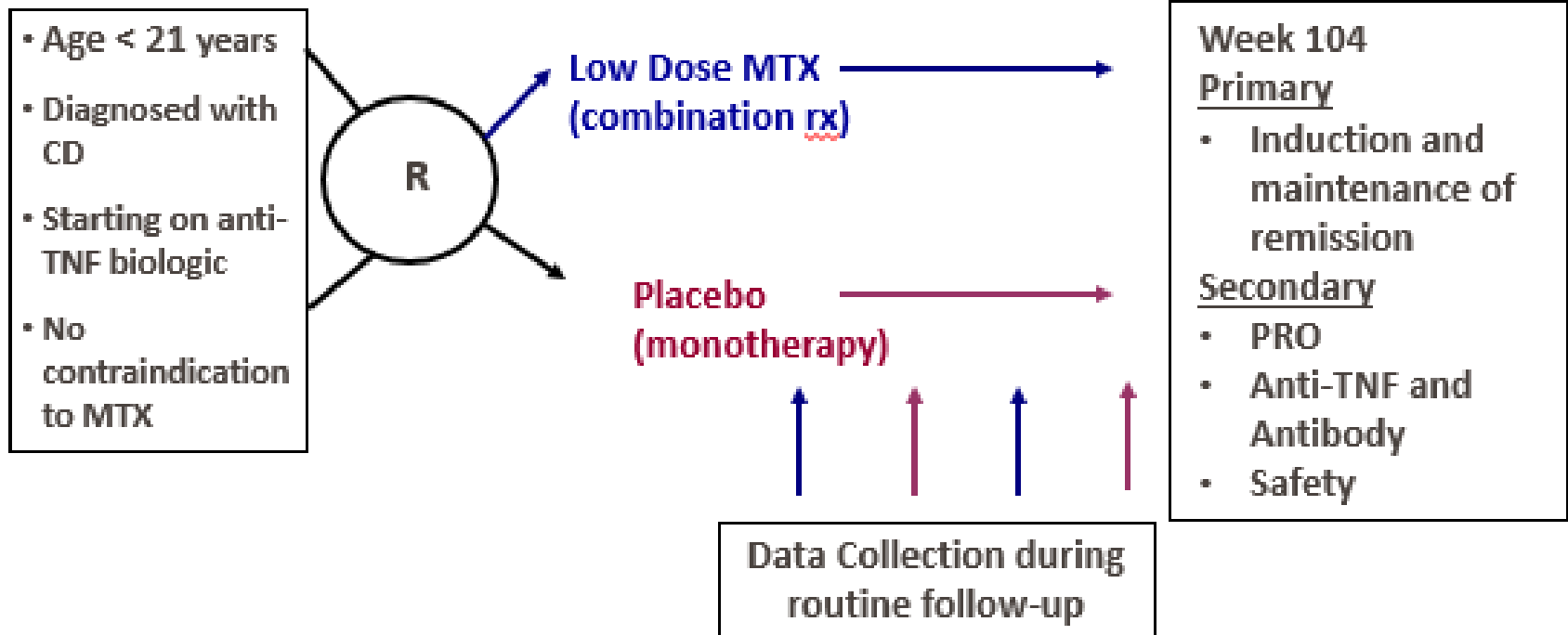
- ▶ Anti-TNF is the most effective treatment for pediatric Crohn's disease
- ▶ Don't work for every patient
- ▶ Don't work forever
- ▶ Real safety concerns

Research Question: In children with Crohn's disease initiating anti-TNF, does combination therapy with a 2nd immune suppressant (methotrexate), as opposed to anti-TNF monotherapy, improve response rate and prolong duration of response with acceptable level of side effects?



**Clinical Outcomes of Methotrexate Binary treatment with Infliximab or adalimumab in practiceE**

# Trial Summary



# Design challenge #1: Subjective nature of many study outcomes

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- ▶ Disease Activity Index and PROs quite subjective
- ▶ Potential threat to validity: knowledge of treatment assignment may impact ascertainment of outcomes
- ▶ Initially considered cluster randomized trial
  - If all of a provider's patients received the same treatment assignment, then he/she would not (inadvertently) ascertain outcomes differently by exposure category
  - Clinician and patient/family stakeholders strongly objected to concept of cluster randomization

# After much deliberation. . .

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**Although generally considered non-pragmatic, we ultimately decided on a randomized, double-blind, placebo controlled trial**

- ▶ Prioritizing internal validity over pragmatism
- ▶ Logistical consideration: requires dispensing medications/placebos directly to patients
  - Most “everyday” clinical settings require high turn-over and don’t have IDS pharmacy
  - Able to identify a mail-order IDS pharmacy with license to ship across state lines



# Design challenge #2: Need for close follow-up

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- ▶ We are supplying a high-risk population with a high-risk treatment
- ▶ Maximizing safety a must!
  - ▶ Careful monitoring of blood counts, liver chemistries, side effects
- ▶ Typical pragmatic trial doesn't have formal follow-up study visits
- ▶ Our concern: if we left follow-up to “routine care” alone, many patients would fall through cracks which would create risk for patients, providers, and study investigators

# Close follow-up is standard of care

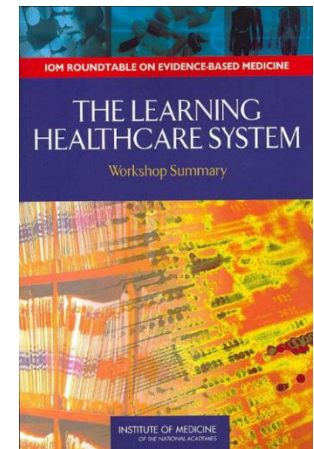
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- ▶ Study protocol specifies a “recommended” visit schedule and lab schedule based on SOC of pediatric CD patients initiating anti-TNF (w or w/out MTX)
  - ▶ Broad windows to reflect routine clinical practice
- ▶ We understand that some visits may be skipped
- ▶ Provide tools to help providers/sites track need for visits
- ▶ Safety check: stop shipments for patients without a visit in 6 months

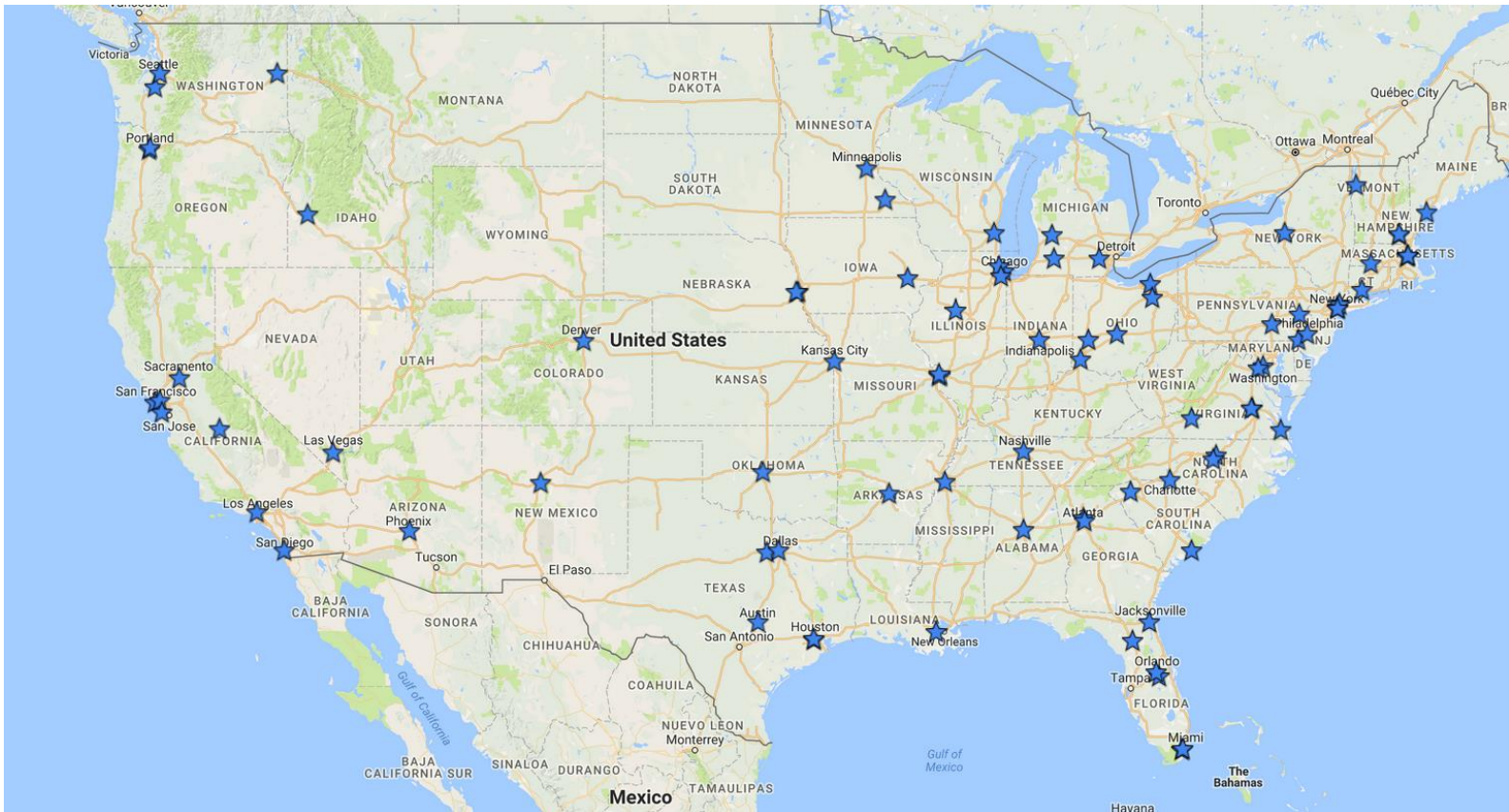
# Curating “Research Grade Data”

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- ▶ Primary outcome suggested in funding announcement: Pediatric Crohn’s Disease Activity Index
  - ▶ Not routinely collected/documentated
- ▶ We designed COMBINE to leverage the ImproveCareNow Network and Registry
  - ▶ Learning Healthcare System established in 2007
  - ▶ QI collaborative + PBRN
  - ▶ Data collected at point of care to support QI and Research



# ImproveCareNow



- **>100 participating practices**
- **40 participating in COMBINE**

# Collecting discrete data at point of care

The screenshot shows an EHR interface with a sidebar on the left containing navigation options like 'Chart Review', 'Care Everywhere', 'Rooming', 'Notes', 'Plan', 'Wrap-Up', 'Charges', 'Communicatio...', 'Sign Visit', 'Results Review', 'Therapy Plans', 'Graphs', 'Review Flows...', 'Request Outsi...', 'Growth Chart', 'Snapshot', 'Medications', and 'Immunizations'. The main content area is titled 'Rooming' and includes a navigation bar with 'Travel Screening', 'Domestic Abuse', 'Fall Assessment', 'Consult Orders', 'Visit Info', 'Vital Signs', and 'Care Everywhere'. The primary section is 'IBD Registry' with the following data collection points:

- Background information:**
  - Current diagnosis: Crohn's disease, ulcerative colitis, indeterminate colitis
  - Has the patient had a complete colectomy? (If correct information appears in the sidebar, it is okay to leave this response blank.) Yes No  unknown
  - Does the patient currently have an ileostomy or colostomy? Yes No  unknown
- Current symptoms:**
  - Describe the IBD symptoms on the WORST day in the last 7 days:
  - General well-being: normal fair poor unknown
  - Limitations in daily activities: no limitations occasional frequent unknown
  - Abdominal pain: none mild moderate to severe unknown
  - Description of abdominal pain: [text input field]
- Stool characteristics:**
  - Describe the stools on the WORST day in the last 7 days:
  - Total number of stools: [input field]  not available/assessed
  - Most stools were: formed partially formed watery unknown
  - Number of liquid/watery stools per day (0 if none): [input field]  not available/assessed
  - Did the patient report bloody stools? Yes No  unknown
  - Did the patient report nocturnal diarrhea? Yes No  unknown
- Extraintestinal manifestations (current):**
  - Fever >38.5 C for 3 of the last 7 days? Yes No  unknown
  - Definite arthritis? Yes No  unknown
  - Uveitis? Yes No  unknown
  - Erythema nodosum? Yes No  unknown
  - Pyoderma gangrenosum? Yes No  unknown

- Centers span 40 unique health systems (or practices)
- EHRs decentralized

# Nothing works (completely) as planned

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## Ongoing challenges

- ▶ Site workload/provider buy-in
- ▶ Missing data
- ▶ Contradictory data
- ▶ Working on data cleaning
  - Prioritizing data related to primary outcome

# Why COMBINE is a pragmatic trial

## Explanatory to Pragmatic continuum

Explanatory	Pragmatic
Double-blind, placebo controlled	Broad eligibility criteria
Pre-specified follow-up windows	Mix of practices and practice types
Outcomes not routinely collected	Mix of provider expertise
	Focus on clinically relevant and patient reported outcomes rather than biomarkers, endoscopic findings
	Protocol flexibility
	Acknowledge issues of adherence (or lack there-of)
	ITT analysis

# We are changing culture

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- ▶ Historically, our specialty has not done large, rigorous clinical trials
  - ▶ Most recent, investigator-initiated controlled clinical trial published in 2000 and included 55 participants
- ▶ Decision making has been the “wild west”
  - ▶ Eminence based
  - ▶ Informed by extrapolation from adult studies and retrospective studies in kids
  - ▶ Lots of heated discussion about theoretical risks and benefits
- ▶ Variation in care rampant!



# Force of change

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- ▶ Channeling passion into action
- ▶ Highly collaborative
- ▶ Constantly learning and sharing best practices
- ▶ An opportunity
  - ▶ To answer a vexing clinical question
  - ▶ To establish process/infrastructure for conducting CER/pragmatic trials in our specialty
  - ▶ **Because we owe this to our patients and their families!**

# Thank You!

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# COMBINE

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## Clinical Outcomes of Methotrexate Binary Therapy in Practice