Pragmatic Recruitment of Underrepresented Groups –
Experience from the Diuretic Comparison Project (DCP)

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VA Boston Cooperative Studies Program Coordinating Center
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Today’s Presentation

• Pragmatic recruitment model
  – Embedded design
  – Multicenter study (without local study investigators and management teams)
  – Broach recruitment (included patients from all 50 States and Puerto Rico)

• Key success factors

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DCP: First full-scale study for the VA Point Of Care Program

Health Systems
- Electronic clinical and administrative data
- Electronic delivery systems
- Healthcare providers
- Patients

VA POC Trials
- Learning Health System
  - Using existing healthcare infrastructure for large RCTs

Managed by the CSP Coordinating Center
Chlorthalidone may be more effective at preventing CV outcomes, but >95% of the VA patients received hydrochlorothiazide for thiazide-type diuretic.

Both drugs have well-established safety profile.

Good fit for a pragmatic design (minimal risk study, less restrictive eligibility criteria and EHR-based safety/outcome monitoring)
DCP: Highly Pragmatic Trial Approach

PRECIS-2 score = 42

Goal: Aimed to recruit ≥13,500 patients across the US

Deliver: Developed EHR-based workflows and integrated with VA primary care

5-point Likert scale to assess 9 research domains
Closer to “5” = more real-world, usual care
DCP Recruitment Procedures

PCP consent was required but clinicians were considered as “NOT engaging in research”

Stay on existing hydrochlorothiazide, or
Switch to dose-equivalent chlorthalidone

- PCP consent
- Patient Consent
- PCP Assent for Randomization
- Patient Randomization
- PCP e-signature for new drug orders

Agreed to have their patients approached for trial recruitment

Confirmed patients could undergo study randomization

Prescribed through usual care (VA outpatient pharmacy)
Provider Entry Screen
Flexible EHR and adaptable user interface
Operational Design
Operated on a scalable EHR infrastructure

Main Medical Center
- Clinical Application Coordinator (CAC) a technician who supports local EHR software integration
- Regional Data Warehouse (RDW) responsible for acquiring EHR data within a regional VA Healthcare System
Operational Design
Adaptable – applied to other regional VA Healthcare Systems
A Centralized EHR-Based Model for the Recruitment of Rural and Lower Socioeconomic Participants in Pragmatic Trials

A Secondary Analysis of the Diuretic Comparison Project

Cynthia Hau, MPH; Jimmy T. Efird, PhD; Sarah M. Leatherman, PhD; Oleg V. Soloviev, MSc; Peter A. Glassman, MD; Patricia A. Woods, MSN; Areef Ihsani, MD; William C. Cushman, MD; Ryan E. Ferguson, ScD
### Recruitment Plan

- **Initiated at** Boston Healthcare System and reached 5 sites within 1st year
- Anticipated other customizations when expanding to regional settings (e.g., max 15 calls to patient, max 3 patient/week for clinician, etc.)

<table>
<thead>
<tr>
<th>Year</th>
<th>Participating VA Healthcare Systems (workflows launched)</th>
<th>Yearly Randomized rate (Monthly average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jun - Dec 2016</td>
<td>1</td>
<td>31 (4)</td>
</tr>
<tr>
<td>2017</td>
<td>5</td>
<td>812 (68)</td>
</tr>
<tr>
<td>2018</td>
<td>23 (added 18)</td>
<td>2,153 (179)</td>
</tr>
<tr>
<td>2019</td>
<td>52 (added 29)</td>
<td>4,020 (335)</td>
</tr>
<tr>
<td>2020</td>
<td>66 (added 14)</td>
<td>3,470 (289)</td>
</tr>
<tr>
<td>2021</td>
<td>72</td>
<td>3,037 (276)</td>
</tr>
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</table>

Total 13,523
Geographic Reach of the Diuretic Comparison Project

Locations of the 72 main VA medical centers
(72 VA Healthcare Systems composed of 72 medical centers and 537 outpatient clinics)

- Alaska
- Hawaii
- Puerto Rico
Geographic Distribution of Randomized Patients

- Urban Residential Areas (55%)
- Rural or Highly Rural Residential Areas (45%)

There were 55 patients from Alaska (not displayed in the figure)
## Key Success Factors

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Electronic Recruitment Workflows (Simplified)

6 major configurations including applications needed outside of the EHR systems

- **Clinician Consent**
  - EHR-integrated consent screen

- **Patient Consent**
  - Eligibility algorithm
  - Data from central mailing & call centers

- **Patient Randomization**
  - EHR-integrated clinician order request
  - Randomization scheme & patient tracking tool
  - VA outpatient pharmacy study drug orders
Web-based Patient Tracking Tool
Established Recruitment Workflows

Prior to integration at the local-level:

- **Study leadership**
  - Performed virtual educational sessions to explain clinicians’ role in this study

- **Internal study team**
  - Partnered with EHR programmers to perform system validation

Manual review of EHR to confirm eligibility
Precis-2 score for recruitment: 4/5
# Key Success Factors

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Recruitment Timeline

Provider capacity
- Fewer “mouse-click” design

Caller skill set and high turnover
- Hired RA dedicated for DCP recruitment

Slow start-up of medical centers
- Engaged VA Central Office to place a higher priority on trials – supporting a learning health system

Pharmacy inventory
- Notified the national clinical pharmacy center

\[ ^{2} \text{Recruitment activity temporarily suspended due to the COVID-19 pandemic.} \]
## Recruitment Efficiency

### No. of study team members for the day-to-day management

<table>
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<th>Number</th>
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<tr>
<td>Callers *</td>
<td>5</td>
</tr>
<tr>
<td>Nurses *</td>
<td>5</td>
</tr>
<tr>
<td>Project managers *</td>
<td>2</td>
</tr>
<tr>
<td>Data manager</td>
<td>1</td>
</tr>
<tr>
<td>Programmers</td>
<td>2</td>
</tr>
<tr>
<td>Informatician</td>
<td>1</td>
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*S 12 Dedicated, 4 on needed basis

### Time needed to complete the required recruitment procedures

<table>
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<th>Procedure</th>
<th>Median no. of days (Q1-Q3)</th>
</tr>
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<tr>
<td>PCP consent</td>
<td>14 (10-23)</td>
</tr>
<tr>
<td>Patient randomization</td>
<td>35 (23-80)</td>
</tr>
<tr>
<td>Eligible → Consented</td>
<td>24 (17-63)</td>
</tr>
<tr>
<td>Consented → Randomized</td>
<td>5 (3-11)</td>
</tr>
<tr>
<td>PCPs signed chlorthalidone orders</td>
<td>2 (0-2)</td>
</tr>
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</table>

### Reflected:

- Workflow generated timely notifications
- Study team responded quickly
- Successfully built a supporting research community
Overall Recruitment

**PCPs**
- 6,448 PCPs identified
- 6,010 PCPs received consent request
- 4,128 (69%) PCPs consented
- 10 sites with 80% PCPs consented

**Patients**
- ~1.4 millions pre-screened
- 16,595 qualified pre-screening and provided verbal consent
- 14,702 verified by study nurses
- 13,523 (92%) patients randomized
- 8% declined randomization by PCPs
## Representation to the VA Healthcare System

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>N = 13,523</td>
</tr>
<tr>
<td>Black¹</td>
<td>2,027 (15%)</td>
</tr>
<tr>
<td>White</td>
<td>10,454 (77%)</td>
</tr>
<tr>
<td>Other</td>
<td>1,042 (8%)</td>
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<thead>
<tr>
<th></th>
<th>Among those with GIS data from EHR</th>
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<tr>
<td></td>
<td>N = 13,497</td>
</tr>
<tr>
<td>South²</td>
<td>5,230 (39%)</td>
</tr>
<tr>
<td>Midwest</td>
<td>4,564 (34%)</td>
</tr>
<tr>
<td>West</td>
<td>1,923 (14%)</td>
</tr>
<tr>
<td>Northeast²</td>
<td>1,585 (12%)</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>156 (1%)</td>
</tr>
<tr>
<td>District of Columbia</td>
<td>39 (0.3%)</td>
</tr>
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</table>

¹ Finding from the VA Office of Health Equity: Black or African American Veterans comprise 16% VHA user in FY16 – FY19.

² Finding from US Census: 43% Veterans from the South and 14% from Northeast.
Collaborate with regulators and medical center leadership:
Ensure trials are aligned with organizational goals and local clinical practice

Collaborate with callers and clinical staff at local level:
Monitor patient status and overall recruitment process

Collaborate with EHR programmers:
Provide technical support for leveraging the existing EHR infrastructure

Collaborate with data warehouse managers:
Develop phenotyping algorithms and perform real-time monitoring of recruitment progress

DCP Conclusions
“No free lunch”, “No one size fits all”, and “No one is above the other”
Conclusion with a Broader Context

• Leveraging health systems for large-scale clinical trials is feasible

• Key elements for successful implementation and execution:

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Conclusion with a Broader Context
Rethinking – expand clinical trial access and reach to underserved patients

Improving:
• Patient representation
• Generalizability of study results
• Research data repository
Helpful Links and DCP Publications

Grand Rounds Oct 2016: Chlorthalidone Versus Hydrochlorothiazide (Frank Lederle, MD)

Grand Rounds May 2018: An Overview of the VA Point of Care Program (Ryan Ferguson, ScD MPH)

Grand Rounds Aug 2022: The Diuretic Comparison Project: A Large Pragmatic Clinical Trial (Areef Ishani, MD, MS)

Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events | NEJM

Design of a pragmatic clinical trial embedded in the Electronic Health Record: The VA's Diuretic Comparison Project | Contemp Clin Trials

A Centralized EHR-Based Model for the Recruitment of Rural and Lower Socioeconomic Participants in Pragmatic Trials | JAMA Network Open

Ascertainment of stroke from administrative data to support a pragmatic embedded clinical trial | Contemp Clin Trials

ProjectFlow: a configurable workflow management application for point of care research | JAMIA Open

Impacts of Research Staff Burnout for a National Large Scale Pragmatic Clinical Trial | Open Access J Clin Trials

The impact of COVID-19 on a large pragmatic clinical trial embedded in primary care | Contemp Clin Trials

Strategies for secondary use of real-world data for outcome ascertainment in pragmatic clinical trials | J Biomed Inform

Practical issues in pragmatic trials: the implementation of the diuretic comparison project | Clin Trials

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DCP Acknowledgement

Co-Authors:
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In memoriam: Frank Lederle, MD

Data and Safety Monitoring Committee:
Drs. Christopher Cannon, Cynthia Coffman, Larry Fine, and Gina Wei
What is next for the VA Point Of Care program?

Upcoming studies

- Creating a Dialysis Platform (DiaP)
- VA CSP #2026 – Beta Blocker Dialyzability on Cardiovascular Outcome (BRAVO)
- VA CSP #2037 – Veterans Affairs Learning Health System Initiative to Assess Novel Screening vs. Usual Care and Treatment with Apixaban vs. Rivaroxaban in Veterans with Atrial Fibrillation (VALIANT-AFib) Trial

Upcoming conference - Seminar series at the Society for Clinical Trials (May 2024 in Boston, MA)

- Lessons learned from DCP
- Overview of the Dialysis Platform
- Incorporating results into clinical practice
Thank you

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