

Office of Research and Development Cooperative Studies Program

U.S. Department of Veterans Affairs

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

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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

Health System	Internal Study Team
Flexible EHR	Systemwide collaboration
Supporting community	Excellent study coordination
Aligned incentives	Creative thinking and rapid adjustment



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



Diuretic Comparison Project (DCP) Jun 2016 – Jun 2022

- 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)



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> N Engl J Med 2022;387:2401-10. DOI: 10.1056/NEJMoa2212270

EDITORIAL

Thiazide-like versus Thiazide Diuretics — Finally, an Answer?

Julie R. Ingelfinger, M.D.

N Engl J Med 2022; 387:2462-2463 DOI: 10.1056/NEJMe2215744

Response by Authors

N Engl J Med 2023; 388:1341-1342 DOI: 10.1056/NEJMc2301922



DCP: Highly Pragmatic Trial Approach PRECIS-2 score = 42



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

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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





DCP Recruitment Results



Original Investigation | Health Informatics

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 Ishani, 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.)

		-
Participating VA Healthcare Systems	Yearly	
(workflows launched)	Randomized rate	
(worknows ladiched)	(Monthly average)	
1	31 (4)	
5	812 (68)	
23 (added 18)	2,153 (179)	– Total
52 (added 29)	4,020 (335)	13,523
66 (added 14)	3,470 (289)	
72	3,037 (276)	
	Participating VA Healthcare Systems (workflows launched) 1 5 23 (added 18) 52 (added 29) 66 (added 14) 72	Participating VA Healthcare Systems (workflows launched) Yearly Randomized rate (Monthly average) 1 31 (4) 5 812 (68) 23 (added 18) 2,153 (179) 52 (added 29) 4,020 (335) 66 (added 14) 3,470 (289) 72 3,037 (276)



Geographic Reach of the Diuretic Comparison Project



Geographic Distribution of Randomized Patients





Key Success Factors

Health System	Internal Study Team
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Electronic Recruitment Workflows (Simplified)

6 major configurations including applications needed outside of the EHR systems





Web-based Patient Tracking Tool

Patient	essigned To Me (0)	Patier	nt Tasks (43	3489) History	Hold	(210)	.ª CS	A2	E Filter by Tasks •
+ Last No	me First Name	Date Of Birth	Mail ID	Next	Home Phone Number	State	Enrolment Status	Institution	X Uncheck All
3		1		- copy comment		1			Check / contact PCP (9)
Global filter									check - CPRS order signed by incorrect PCP (5)
•						KENTUCKY	STATUS NOT AVAILABLE		Confirm correct PCP for patient (25) CPRS order declined (3)
4 .	Script • ques Information u	tions part 1: pdate	receiving letter	DCP_patter	L_consentBy	(Phone hus			Eligibility check (4) Information update (657)
•						HAWAII	CHLORTHALIDONE		Information update (26394) C Look at order in CPRS and make decision (1)
	Information up	pdate	DCP_pa6	ent_updateStatus					Medication orders complete, verify CPRS to proceed to (1)
> 14			DCP path	ent_providerApprova	AndRandom	nization			No PCP consented at this time (20)
*									



Established Recruitment Workflows



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

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



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Recruitment Timeline

^a Recruitment activity temporarily suspended due to the COVID-19 pandemic.



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	VA



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Recruitment Efficiency

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

5 Callers *

5 Nurses *

2 Project managers *

1 Data manager

2 Programmers

1 Informatician

* 12 Dedicated, 4 on needed basis

Time needed to complete the required recruitment procedures	Median no. of days (Q1-Q3)
PCP consent	14 (10-23)
Patient randomization	35 (23-80)
Eligible \rightarrow Consented	24 (17-63)
Consented → Randomized	<mark>5</mark> (3-11)
PCPs signed chlorthalidone orders	<mark>2</mark> (0-2)
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



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

Total randomized	N = 13,523
Black ¹	2,027 (15%)
White	10,454 (77%)
Other	1,042 (8%)
Among those with GIS data from EHR	N = 13,497
South ²	5,230 (39%)
Midwest	4,564 (34%)
West	1,923 (14%)
Northeast ²	1,585 (12%)
Puerto Rico	156 (1%)
District of Columbia	39 (0.3%)

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.



DCP Conclusions

"No free lunch", "No one size fits all", and "No one is above the other"

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

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

Project managers and study nurses **Collaborate with regulators and medical center leadership:** Ensure trials are aligned with organizational goals and local clinical practice



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

Programmers and software developers



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

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 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 ***



DCP Acknowledgement

Co-Authors:

Cynthia Hau, Jimmy Efird, Sarah Leatherman, Oleg Soloviev, Peter Glassman, Patricia Woods, Areef Ishani, William Cushman, and Ryan E. Ferguson

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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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