VA | U.S. Department of Veterans Affairs

Pragmatic Clinical Trials at the VA – The Diuretic Comparison Project

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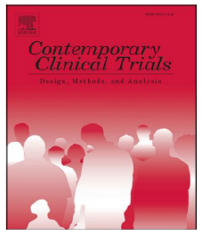
The VA Point of Care Program

- GOAL: large, inexpensive RCTs
- Optimize use of EMRs
- Avoid the cost of the “clinical trial apparatus”
- Recruitment/randomization “at the point of care” (that’s not how we’re doing it!)
- Outcomes from EMRs
- DCP is the first full scale RCT in this program

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Check for updates

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

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Chairmen: Areef Ishani, MD MS
Minneapolis, VAMC
William C. Cushman, MD
Memphis, VAMC

CSP Center: Ryan E. Ferguson, ScD MPH
MAVERIC, Boston VAMC

Diuretic Comparison Project: Study Question

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

- Network meta-analysis:
  - 21% in MACE for CTD vs. HCTZ
  - 18% ↓ when adjusted for attained BP

(Roush, HTN 2012; 59:1110-7)

Inclusion criteria

1. Over the age of 65 years (half outcomes outside VA)
2. On HCTZ 25 or 50 mg/d from VA (not combo)
3. Most recent SBP (in CPRS) ≥ 120 mm Hg

Study Intervention

- Patients currently treated with HCTZ
- Open-label randomization to remain on their current dose HCTZ (25 or 50 mg), or convert them half that dose of CTD (12.5 or 25 mg)

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

DCP Adverse Events

- Discontinuation of the study diuretic
- Hospitalization for (1° dx): ↓K, ↓Na, renal failure
- Renal failure (doubling of Cr, begin dialysis, vascular access for dialysis, renal transplant)
- Other recorded K<3.1 or Na<130
- New diabetes

Stats/Sample Size

- The study uses the intent to treat principle and all randomized patients are include
- All patients are followed until withdrawal, death, or the end of the study
- Patient follow-up continues beyond reaching a primary endpoint to determine secondary and safety outcomes and recurrent events
- The study had one planned interim analysis after the 500th event occurred. Using the O-Brien Fleming procedure, the primary hypothesis was tested with a two-sided log-rank test with a type I error of 0.1%
- The primary hypothesis will be tested with an unadjusted time-to-event analysis with a two-sided log-rank test.
- Study follow-up will end after the 1055th event.
- We posit an event rate of 13.5% of the composite outcome in the hydrochlorothiazide group and 11.1% in the CTD group.
- The primary statistical analysis will have 90% power and two-sided 4.9% type I error to detect a hazard ratio of 1.22 or larger or 0.82 or less.

Pragmatic Nature

- All study related tasks done by central staff (Boston or Minneapolis)
- No study staff at any site
- Centralized:
  - Recruitment
  - Consenting
  - Randomization
  - Filling out drug order
  - Assessing outcomes
- Usual Care
  - Signing drug order
  - Filling prescription
  - Managing study drug and hypertension

APPROACH

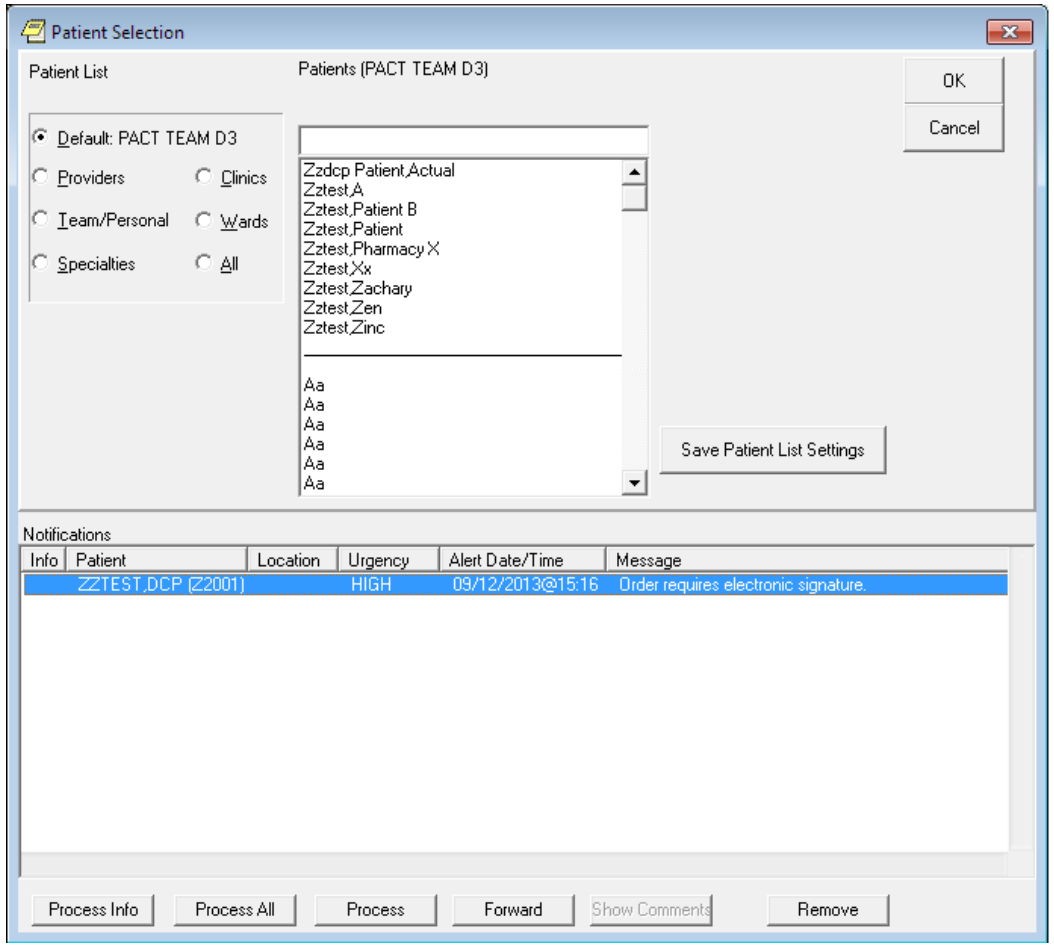
Obstacles

- Enrolling Medical Centers
  - No local site investigator to push the study at each site. Has been difficult to get sites to agree to participate
    - Worry about additional burden on PCPs
    - Competing interests from other high priority items – so feel DCP would be a distraction to leadership
  - Memorandum signed by Chief of Staff, Chief of Research and Chief of Pharmacy
- Enrolling PCPs
  - Work load concerns – particularly alerts
  - IRB considered providers and subjects – required provider consent
- Embedding the work flow of the study into clinical operations

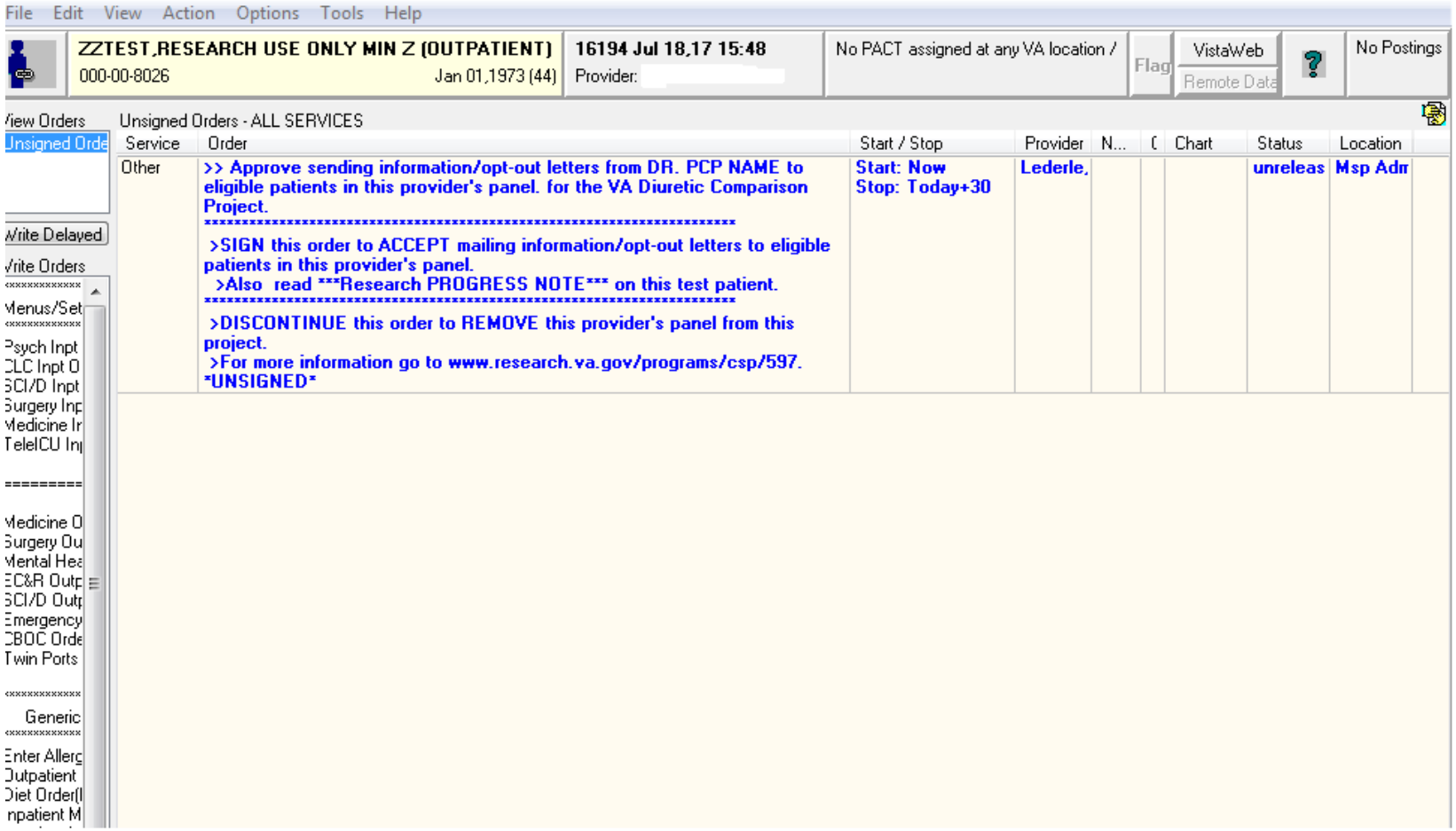
What Are We Asking You For? (Every click is sacred)

- Initial Provider Inclusion (1 time for entire study)
  - 1 view alert per provider to enroll entire panel
  - 1 order to include your patients
- Per Patient
  - 1 order to randomize
  - 1 order for the drug (of randomized to chlorthalidone)/ 0 orders if they remain on HCTZ
- Median provider has 3 patients in the study
- Total of 6 view alerts over the entire study

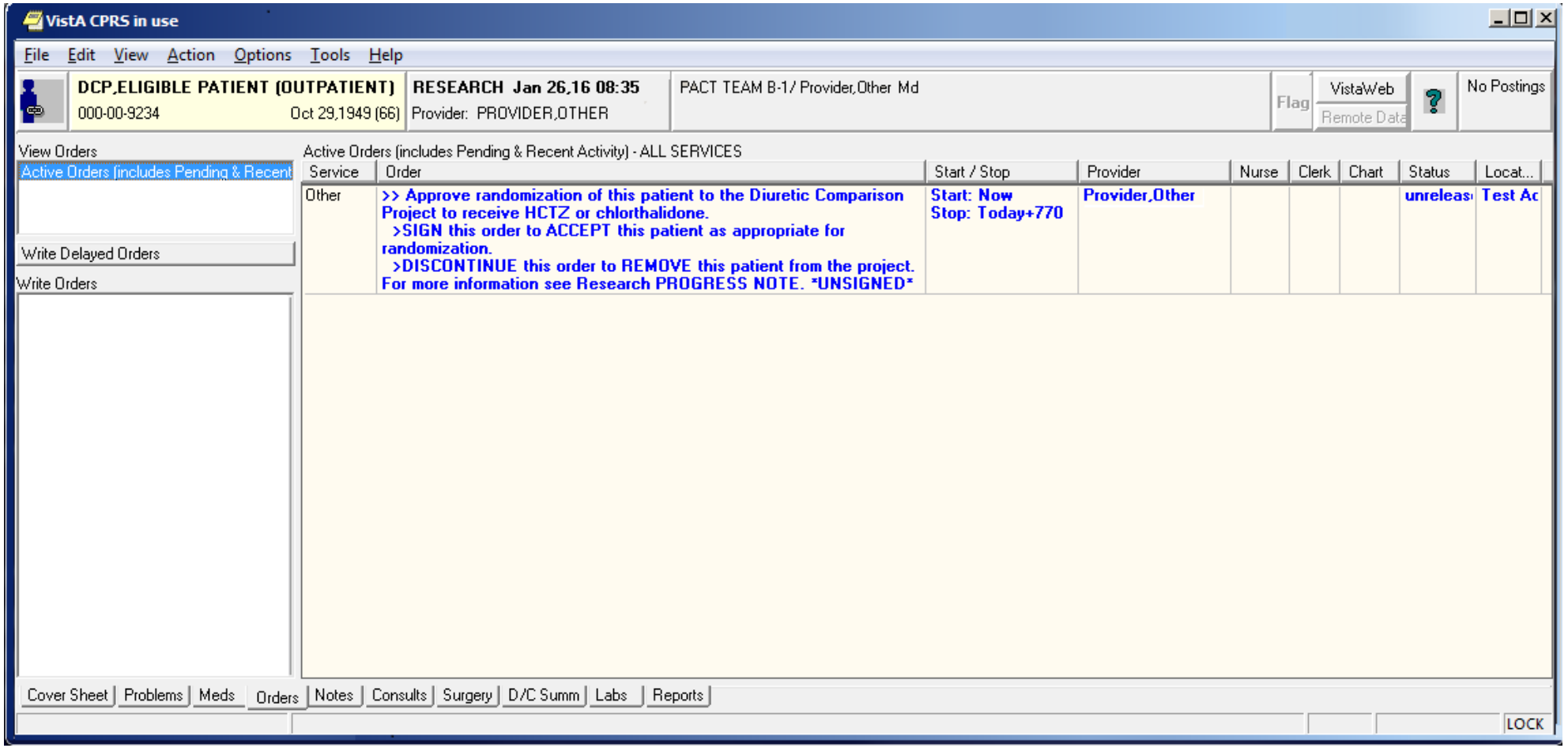
View Alert for Approval to Recruit Patients in PCP's Panel



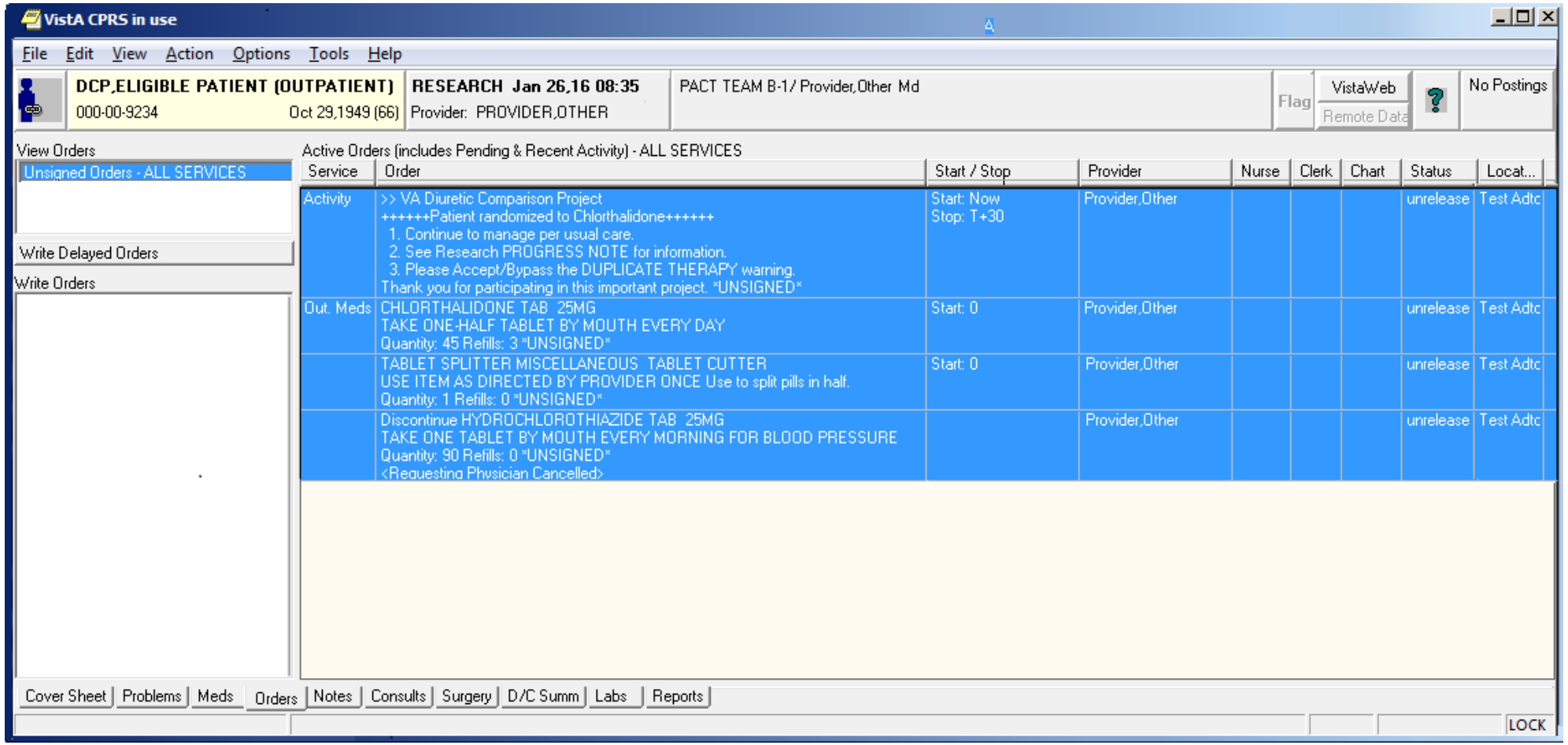
Order to Screen/Recruit Eligible Patients in PCP's Panel



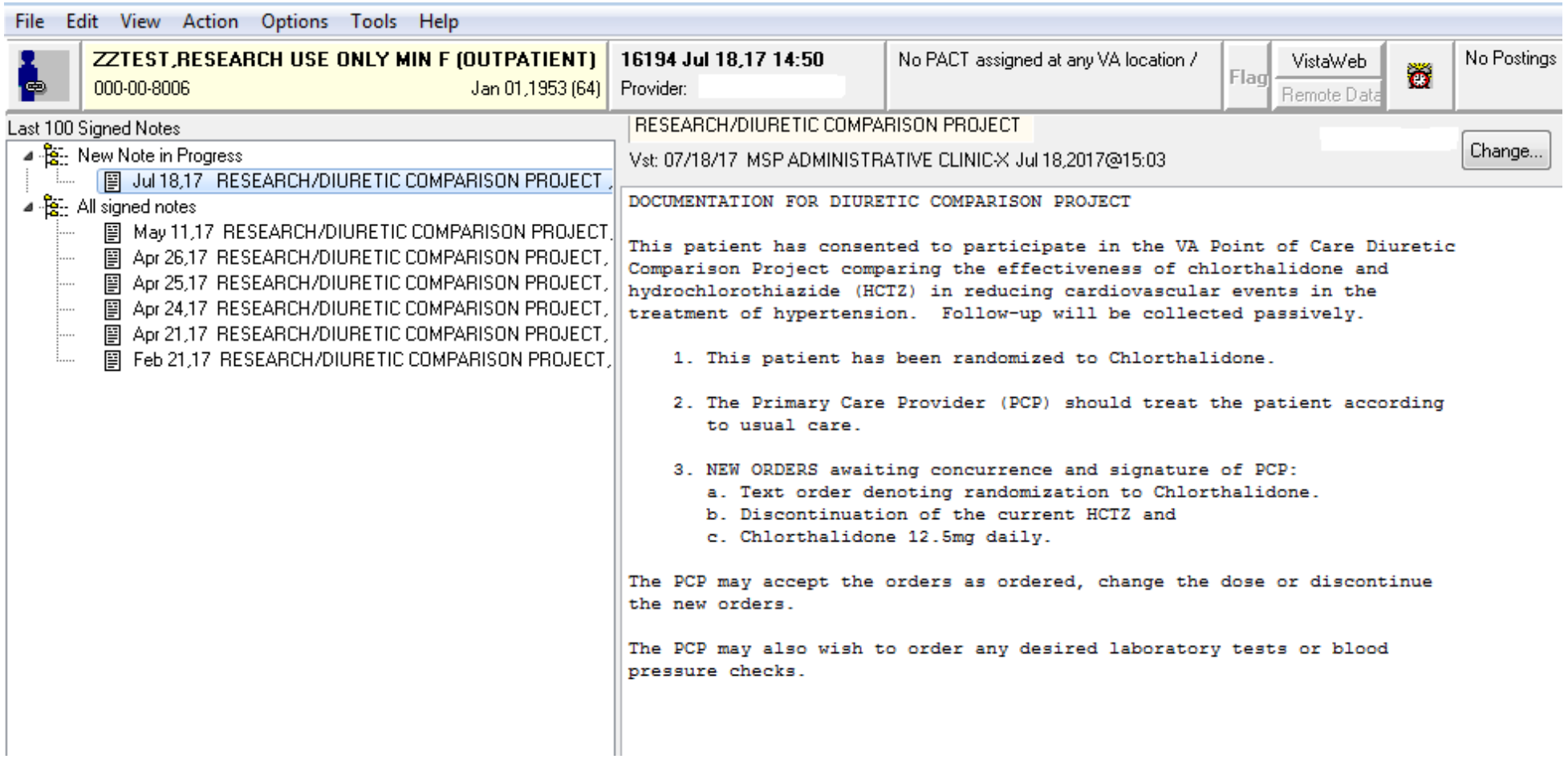
Once a Patient Consents: PCP Approval to Randomize



Randomization Orders

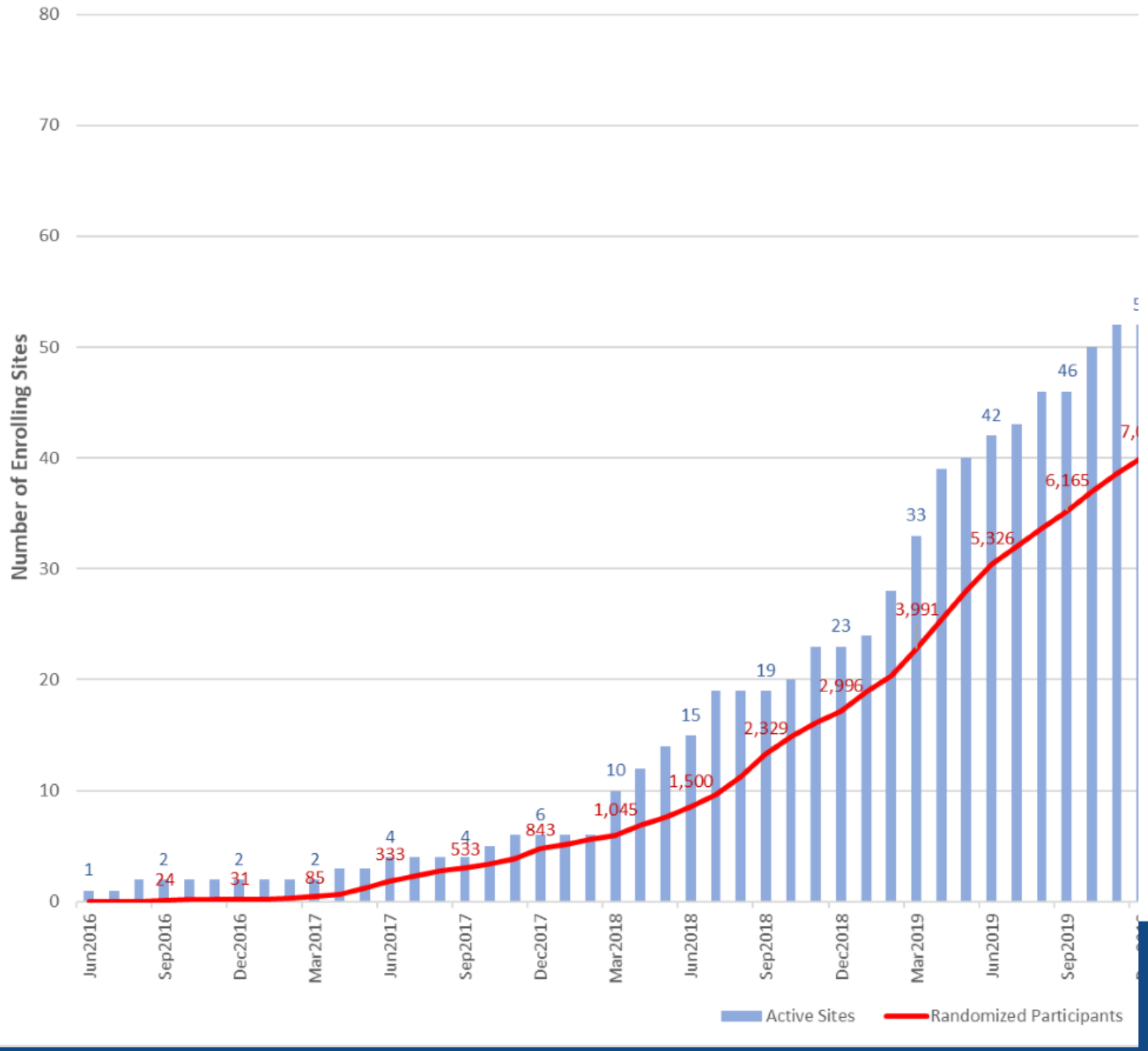


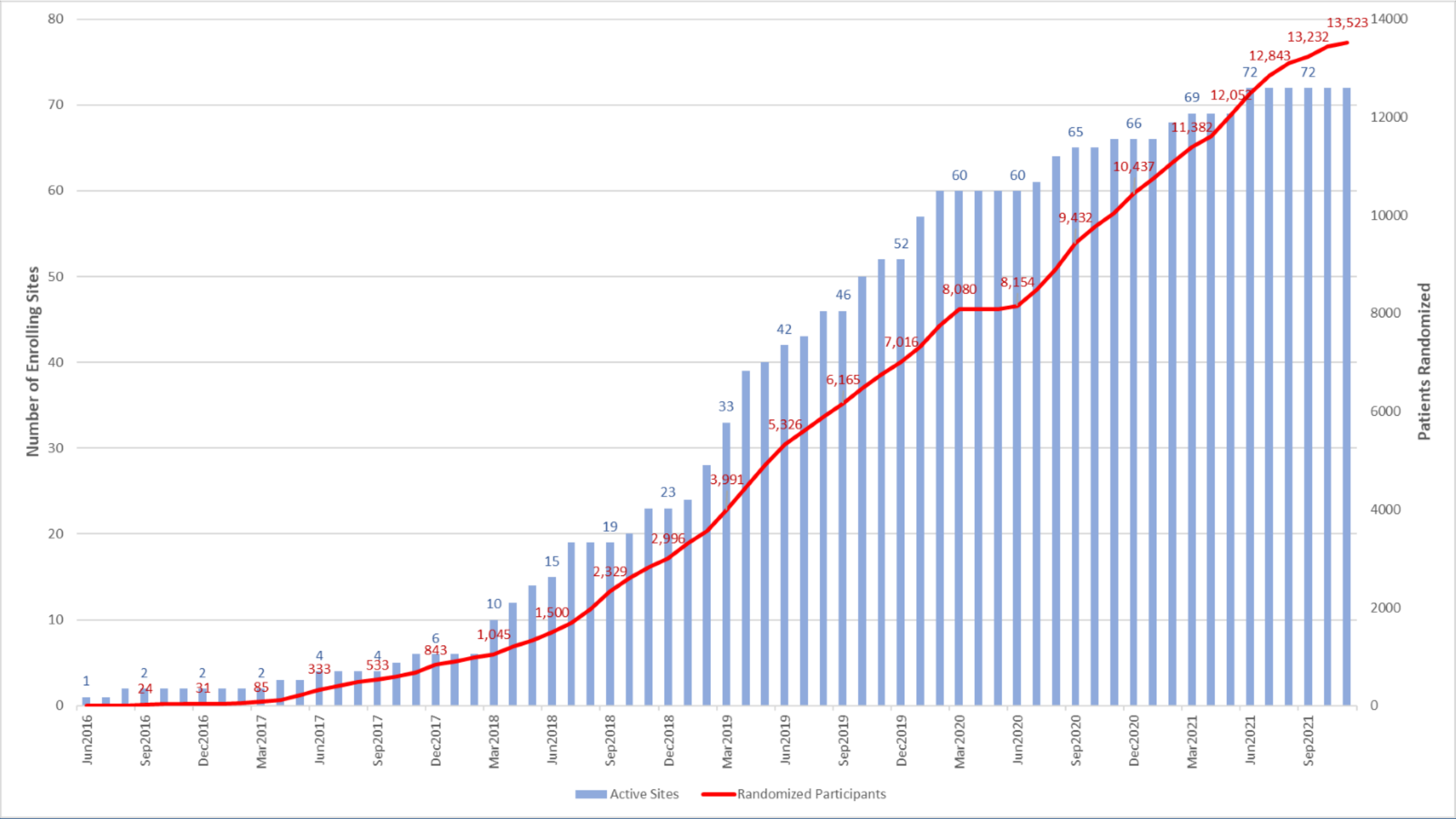
Randomization Note



Obstacles (cont)

- Call Center
  - Initially contracted with existing VA call center
  - No prior research experience
  - They had other priorities
- Mid study – started our own dedicated call center in Minneapolis


Number of Enrolling Sites
80
70
60
50
40
30
20
10
0
1
2
2
2
4
4
6
10
15
19
23
33
42
46
24
31
85
333
533
843
1,045
1,500
2,329
2,996
3,991
5,326
6,165
Jun2016
Sep2016
Dec2016
Mar2017
Jun2017
Sep2017
Dec2017
Mar2018
Jun2018
Sep2018
Dec2018
Mar2019
Jun2019
Sep2019
Active Sites
Randomized Participants


Number of Enrolling Sites
Patients Randomized
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10
20
30
40
50
60
70
80
0
2000
4000
6000
8000
10000
12000
14000
1
2
2
2
4
4
6
10
15
19
23
33
42
46
52
60
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65
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69
72
72
24
31
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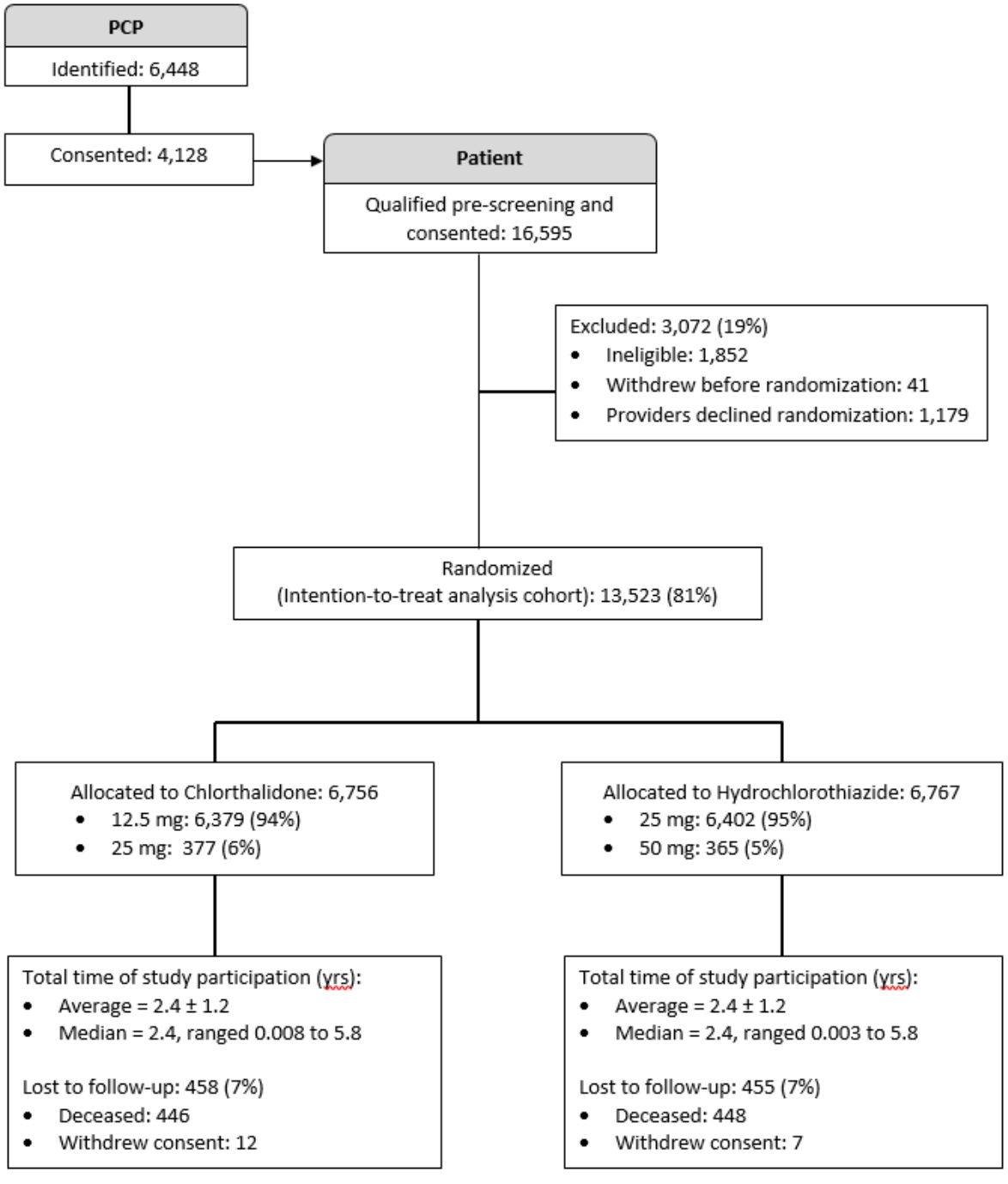
7,016
8,080
8,154
9,432
10,437
11,382
12,052
12,843
13,232
13,523
Jun2016
Sep2016
Dec2016
Mar2017
Jun2017
Sep2017
Dec2017
Mar2018
Jun2018
Sep2018
Dec2018
Mar2019
Jun2019
Sep2019
Dec2019
Mar2020
Jun2020
Sep2020
Dec2020
Mar2021
Jun2021
Sep2021
Active Sites
Randomized Participants


Recruitment sites
Guam
Northern Mariana Islands
Puerto Rico
American Samoa
United States Virgin Islands

Figure 1. CONSORT diagram for the Diuretic Comparison Project (DCP)



68.5% of approached providers consented to participate!!

72 Medical Centers – plus affiliated clinics

4,128 PCP

13,523 Participants

18 Staff members

Boston

				Contacted		Consent requested		Consented		Declined	
#	Site#	Launch Date	#PCPs identified	N	% of identified	N	% of contacted	N	% of consent requested	N	% of consent requested
	Overall:		**6,448**	**6,188**	**96.0%**	**6,007**	**97.1%**	**4,113**	**68.5%**	**1,412**	**23.5%**
1	Boston	06/17/2016	91	91	100.0%	88	96.7%	66	75.0%	17	19.3%
2	MSP	01/19/2017	199	194	97.5%	185	95.4%	158	85.4%	22	11.9%
3	614	04/26/2017	98	98	100.0%	98	100.0%	69	70.4%	15	15.3%
4	LA	07/01/2017	244	244	100.0%	225	92.2%	156	69.3%	48	21.3%
5	541	10/18/2017	185	185	100.0%	180	97.3%	121	67.2%	47	26.1%
6	578	01/17/2018	122	122	100.0%	121	99.2%	81	66.9%	28	23.1%
7	Portland	3/03/2018	145	145	100.0%	143	98.6%	90	62.9%	37	25.9%
8	600	03/15/2018	100	100	100.0%	99	99.0%	67	67.7%	28	28.3%
9	402	03/21/2018	77	77	100.0%	75	97.4%	57	76.0%	13	17.3%
10	608	03/21/2018	47	47	100.0%	47	100.0%	31	66.0%	10	21.3%
11	405	05/02/2018	74	74	100.0%	74	100.0%	60	81.1%	10	13.5%
12	437	05/02/2018	43	43	100.0%	42	97.7%	27	64.3%	13	31.0%
13	558	05/25/2018	125	125	100.0%	125	100.0%	82	65.6%	34	27.2%
14	657	06/02/2018	216	188	87.0%	119	63.3%	71	59.7%	42	35.3%
15	518	06/08/2018	33	33	100.0%	30	90.9%	15	50.0%	10	33.3%
16	573	07/10/2018	219	219	100.0%	213	97.3%	123	57.7%	75	35.2%
17	St Cloud	07/18/2018	65	65	100.0%	65	100.0%	47	72.3%	15	23.1%

								Consented		Eligible for randomization		Randomized	
#	Site#	Site Launch Date	Patients identified	Failed pre-screen	Qualified pre-screen	Completed contact	Expected randomized [3]	n	% of expected	n	% of expected	n	% of expected
	Overall		**1,399,571**	**1,331,984**	**67,587**	**42,487**	**23,682**	**16,276**	**68.7%**	**13,449**	**56.8%**	**13,232**	**55.9%**
1	Boston	06/17/2016	16,091	15,248	843	731	296	153	51.7%	135	45.6%	135	45.6%
2	MSP	01/19/2017	47,533	44,676	2,857	2,451	1,000	832	83.2%	735	73.5%	733	73.3%
3	614	04/26/2017	21,517	20,291	1,226	1,019	430	251	58.4%	216	50.2%	212	49.3%
4	LA	07/01/2017	30,340	29,034	1,306	1,061	457	254	55.6%	198	43.3%	197	43.1%
5	541	10/18/2017	50,024	47,425	2,599	2,119	910	466	51.2%	377	41.4%	375	41.2%
6	578	01/17/2018	20,964	19,789	1,175	946	412	241	58.5%	203	49.3%	201	48.8%
7	Portland	03/2018	29,025	27,630	1,395	1,104	489	408	83.4%	342	69.9%	339	69.3%
8	600	03/15/2018	17,479	16,859	620	441	217	128	59.0%	104	47.9%	103	47.5%
9	402	03/21/2018	21,141	20,061	1,080	844	378	291	77.0%	253	66.9%	251	66.4%
10	608	03/21/2018	10,319	9,795	524	377	184	113	61.4%	88	47.8%	87	47.3%
11	405	05/02/2018	11,133	10,367	766	615	269	261	97.0%	204	75.8%	204	75.8%
12	437	05/02/2018	15,143	14,537	606	606	213	200	93.9%	171	80.3%	171	80.3%
13	558	05/25/2018	24,575	22,807	1,768	1,234	619	456	73.7%	387	62.5%	387	62.5%
14	657	06/02/2018	18,370	17,390	980	773	343	216	63.0%	178	51.9%	176	51.3%
15	518	06/08/2018	4,628	4,434	194	148	68	47	69.1%	35	51.5%	35	51.5%
16	573	07/10/2018	48,293	46,167	2,126	1,513	745	611	82.0%	498	66.8%	495	66.4%
17	St Cloud	/18/2018	19,002	17,953	1,049	831	367	400	109.0%	345	94.0%	343	93.5%

Baseline demographics and medical history.

Characteristic	$N = 13,523$
Baseline demographics	
Age (yrs), mean ± SD	72.4 ± 5.3
Male, n (%)	13,092 (96.8%)
Race, n (%)	
Asian	28 (0.2%)
Black	2072 (15.0%)
White	10,450 (77.3%)
Other or multiple race	296 (2.2%)
Unknown	722 (5.3%)
Ethnicity, n (%)	
Hispanic or Latino	494 (3.7%)
Not Hispanic or Latino	12,549 (92.8%)
Multiple ethnicity	2 (0.0%)
Unknown	478 (3.5%)
Baseline HCTZ dose, n (%)	
25 mg	12,784 (94.5%)
50 mg	739 (5.5%)
Height (cm), mean ± SD	176.4 ± 7.4
Weight (kg), mean ± SD	99 ± 19.5
BMI (kg/m^2), mean ± SD	31.8 ± 5.8
Systolic Blood Pressure (mmHg), mean ± SD	138.9 ± 13.7
Diastolic Blood Pressure (mmHg), mean ± SD	76.7 ± 9.1
Potassium (mmol/L), mean ± SD	4.1 ± 0.4
Sodium (mmol/L), mean ± SD	139.1 ± 2.7
SCr (mg/dL), mean ± SD	1.1 ± 0.3
eGFR*, mean ± SD	72.5 ± 19.4

- 55% of randomized patients lived in a rural location

Baseline demographics and medical history.

Characteristic	$N = 13,523$
Baseline demographics	
Age (yrs), mean ± SD	72.4 ± 5.3
Male, n (%)	13,092 (96.8%)
Race, n (%)	
Asian	28 (0.2%)
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25 mg	12,784 (94.5%)
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Height (cm), mean ± SD	176.4 ± 7.4
Weight (kg), mean ± SD	99 ± 19.5
BMI (kg/m^2), mean ± SD	31.8 ± 5.8
Systolic Blood Pressure (mmHg), mean ± SD	138.9 ± 13.7
Diastolic Blood Pressure (mmHg), mean ± SD	76.7 ± 9.1
Potassium (mmol/L), mean ± SD	4.1 ± 0.4
Sodium (mmol/L), mean ± SD	139.1 ± 2.7
SCr (mg/dL), mean ± SD	1.1 ± 0.3
eGFR*, mean ± SD	72.5 ± 19.4

Medical history	
Any prior cardiovascular event[†], n (%)	2555 (18.9%)
Stroke, n (%)	1011 (7.5%)
Myocardial infarction, n (%)	419 (3.1%)
Congestive heart failure, n (%)	983 (7.3%)
Unstable angina, n (%)	622 (4.6%)
Urgent coronary revascularization, n (%)	311 (2.3%)
Chronic kidney disease, n (%)	3539 (26.2%)
Diabetes[‡], n (%)	6029 (44.6%)
Hypokalemia, n (%)	1414 (10.5%)
Hyponatremia, n (%)	373 (2.8%)
Gout	1754 (13.0%)

Concomitant medications at baseline*.

Medication	N = 13,523
Antihypertensive agents	
ACE inhibitors, n (%)	5008 (37.0%)
Alpha blockers, n (%)	1416 (10.5%)
Angiotensin II inhibitor, n (%)	3787 (28.0%)
Antihypertensive combinations†, n (%)	76 (0.6%)
Beta blockers, n (%)	5405 (40.0%)
Calcium channel blockers, n (%)	5545 (41.0%)
Combination diuretics‡, n (%)	252 (1.9%)
Loop diuretics, n (%)	311 (2.3%)
Other thiazides or diuretics§, n (%)	2 (0.0%)
Other antihypertensives‖, n (%)	524 (3.9%)
Number of drug classes prescribed in addition to HCTZ§, n (%)	
0	1589 (11.8%)
1	4359 (32.2%)
2	4363 (32.3%)
3	2343 (17.3%)
4	686 (5.1%)
≥ 5	183 (1.4%)

	Baseline (N = 13,232)	Month 6 (N = 11,200)	Month 12 (N = 8,885)	Month 18 (N = 7,747)
Patients with BP measures [1]	N = 13,232 (100%)	N = 8,496 (76%)	N = 6,440 (72%)	N = 5,233 (68%)
SBP (mmHg) Mean ± SD (Range) (Q1 - Q3)	138.9 ± 13.7 (101 - 238) (129 - 146)	135.6 ± 15.8 (58 - 213) (126 - 144)	135.7 ± 16.1 (70 - 214) (126 - 145)	136 ± 16.5 (76 - 226) (126 - 145)

	Month 24 (N = 5,733)	Month 30 (N = 3,476)	Month 36 (N = 1,970)	Month 42 (N = 937)
Patients with BP measures [1]	N = 3,657 (64%)	N = 2,338 (67%)	N = 1,294 (66%)	N = 579 (62%)
SBP (mmHg) Mean ± SD (Range) (Q1 - Q3)	135.8 ± 16.6 (67 - 215) (126 - 145)	136 ± 17.2 (64 - 220) (125 - 146)	137 ± 16.6 (94 - 214) (127 - 146)	136.5 ± 16.5 (88 - 200) (127 - 146)

	Baseline [1] (N = 13,232)	Month 6 (N = 11,200)	Month 12 (N = 8,885)	Month 18 (N = 7,747)
Patients with fill records [2]	N = 13,175 (99.6%)	N = 10,641 (95%)	N = 8,087 (91%)	N = 6,640 (85.7%)
Continued with randomized drug	-	10,159 (95.5%)	7,595 (93.9%)	6,169 (92.9%)

	Month 24 (N = 5,733)	Month 30 (N = 3,476)	Month 36 (N = 1,970)	Month 42 (N = 937)
Patients with fill records [2]	N = 4,659 (81.3%)	N = 2,710 (78%)	N = 1,473 (74.8%)	N = 692 (73.9%)
Continued with randomized drug	4,290 (92.1%)	2,476 (91.4%)	1,326 (90.0%)	608 (87.9%)

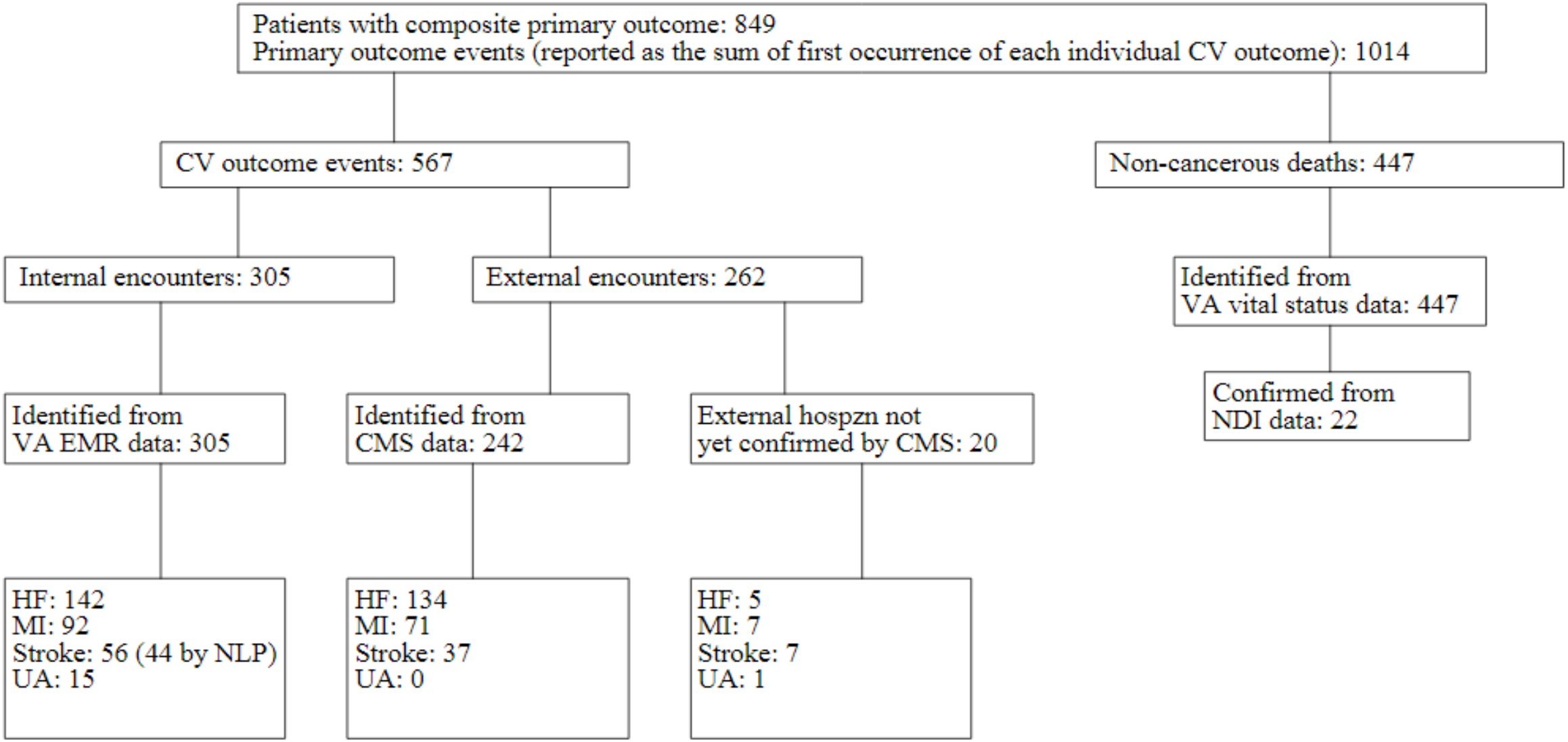
Outcomes

- Outcomes were ascertained through a combination of manual adjudication, algorithms for primary outcome events excluding non-cancer death, National Death Index for non-cancer death, and natural language processing (NLP) for stroke.

Data Source	Dates Available
Corporate data warehouse (EHR)	2016 – 2022
Medicare – annual	2016 – 2020
Medicare – quarterly	2021
National Death Index	2016 – 2019

	No. (%) with Outcomes
	Randomized (n=13,523)
Primary outcome	1,260 (9.4%)
Secondary outcomes	
Non-cancer deaths	636 (4.7%)
Acute congestive heart failure	443 (3.3%)
Myocardial infarction	261 (2.0%)
Stroke	153 (1.2%)
Unstable angina with urgent coronary revascularization	31 (0.3%)

Figure C2. Primary Outcome Event Flow Diagram



DCP Conclusions

- Pragmatic Trials are possible to successfully perform in the VA
- Comparative effectiveness studies are likely the easiest to implement
- Enrolled a broad sample of patients that are typically unavailable to traditional clinical trials
- Broad recruitment enhances generalizability of study results

Thanks

Minneapolis

- Srihari Raju
- Eustacia Ikeri
- Olivia Taylor
- Jacob McPherson
- Katherine Perkey
- Abhinav Tella
- Alicia Zhang
- William Vang

- Boston
  - Ryan Ferguson
  - Sarah Leatherman
  - Patricia Woods
  - Christal Sadatis
  - Maura Flynn
  - Alison Klint
  - Amanda Guski
  - Robert Lew
  - Cynthia Hau

Memphis

- Bill Cushman

Steering Committee

- Addison Taylor
- Peter Glassman
- Mary Brophy
- Louis Fiore

Dialysis Platform Study (DIAP) Beta Blocker Dialyzability on Cardiovascular Outcomes (BRAVO)

- Chairs
- Areef Ishani areef.Ishani@va.gov
- James Kaufman jimbobboy@gmail.com

Dialysis Platform (DiaP)

- The Dialysis Platform (DiaP) will provide an infrastructure to support sequential and concurrent randomized clinical trials relevant to the VA dialysis population with a primary focus on comparative effectiveness trials.
- DiaP will include a prospective registry of all VA dialysis patients (facility and CITC)
  - Prevalent and incident patients
  - and who have a primary care provider at the VA and receive their medications at the VA

DiaP cont

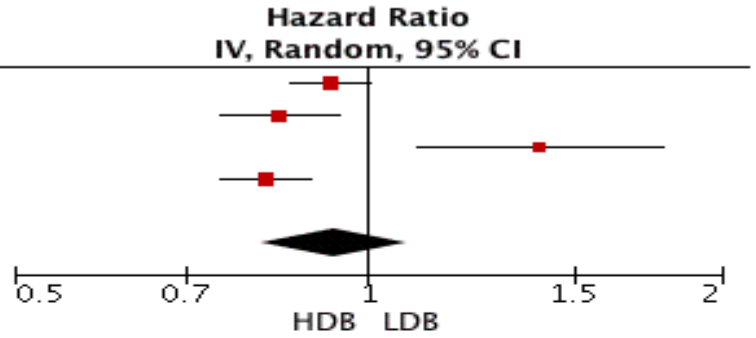
- Platform for interested investigators to submit projects for review and implementation, to identify and enroll potential participants, collect necessary trial data, and assist in data analysis and manuscript preparation

Why do the study?

All-cause Mortality - hazard ratios

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Assimon	-0.0726	0.0399	29.0%	0.93 [0.86, 1.01]
Shireman	-0.1744	0.0598	26.1%	0.84 [0.75, 0.94]
Weir	0.3365	0.123	16.6%	1.40 [1.10, 1.78]
Wu	-0.1985	0.0455	28.3%	0.82 [0.75, 0.90]
Total (95% CI)			**100.0%**	**0.94 [0.81, 1.08]**

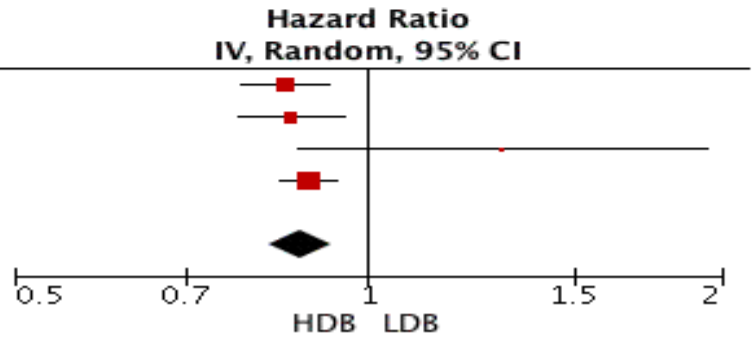
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 18.96$, df = 3 (P = 0.0003); $I^2 = 84\%$
Test for overall effect: Z = 0.93 (P = 0.35)



Cardiovascular Events - hazard ratios

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Assimon	-0.1625	0.0438	30.0%	0.85 [0.78, 0.93]
Shireman	-0.1508	0.0531	23.4%	0.86 [0.78, 0.95]
Weir	0.2624	0.2047	2.2%	1.30 [0.87, 1.94]
Wu	-0.1165	0.0295	44.4%	0.89 [0.84, 0.94]
Total (95% CI)			**100.0%**	**0.88 [0.83, 0.93]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.59$, df = 3 (P = 0.20); $I^2 = 35\%$
Test for overall effect: Z = 4.17 (P < 0.0001)



BRAVO

- Pragmatic trial in hemodialysis patients comparing metopolol succinate qd vs carvedilol bid
  - Inclusion: patient on beta blocker at baseline – will convert
- Event Driven: 1100 events (anticipate 2200 over 4.5 years)
- Outcome: Cardiovascular outcomes, hypotension, falls
  - Outcomes from EMR and claims data
  - Pragmatic trial – no forms, no study visits, minimal inclusion/exclusion criteria

- Goal: every VA dialysis unit participating in the trial

Conclusion

- Lots of potential for pragmatic trials at the VA
- Particularly comparative effectiveness studies

Another potential study

- Randomized Evaluation of Sodium Dialysis Levels of Vascular Events (RESOLVE)
- International pragmatic trial
- Dialysis sites randomized dialysis sodium 137mmol/l vs 140mmol/l
- Outcomes: Major cardiovascular events or death
- Follow up duration 5 years