Annals of Internal Medicine

IDEAS AND OPINIONS

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

Frank A. Lederle, MD; William C. Cushman, MD; Ryan E. Ferguson, ScD, MPH; Mary T. Brophy, MD, MPH; and Louis D. Fiore, MD, MPH

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Minneapolis VAMC

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CSP Coordinating Center: MAVERIC, Boston VAMC

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The VA Point of Care Program

- Engineering a Learning Health Care System by Ryan Ferguson, 6/21/13
- Goal: large inexpensive RCTs
- Optimize use of EMRs
- Avoid the cost of “the clinical trial apparatus”
- Recruitment/randomization at the point of care
- Outcomes from EMRs

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The VA Point of Care Program

CLINICAL TRIALS DESIGN

Clinical Trials 2011; **8:** 183–195

A point-of-care clinical trial comparing insulin administered using a sliding scale *versus* a weight-based regimen

Louis D Fiore[a,b,c], Mary Brophy[a,c], Ryan E Ferguson[a,b], Leonard D'Avolio[a,d], John A Hermos[illegible] O'Neil Jr[a] Matthew

Implementation of the Department of Veterans Affairs' first point-of-care clinical trial

J Am Med Inform Assoc 2012;**19**:e170—e176.

Leonard D'Avolio,[1,2,3] Ryan Ferguson,[1] Sergey Goryachev,[1] Patricia Woods,[1] Thomas Sabin,[1] Joseph [illegible] Jasmine Escalera,[1] Mary [illegible]

CLINICAL TRIALS ARTICLE

Clinical Trials 2014; **11:** 292–299

Veterans Healthcare Administration providers' attitudes and perceptions regarding pragmatic trials embedded at the point of care

Charlene R Weir[a,b], Jorie Butler[a], Iona Thraen[a], Patricia A Woods[c], John Hermos[c,d], Ryan Ferguson[c,e], Theresa Gleason[f], Robyn Barrus[a] and Louis Fiore[c,d,e]

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Point of Care - Challenges

- Early experiments showed the informatics nearly ready to go, but the trials did not “scale up”
  - ‘Point of Care’ means primary care provider (PCP) must take extra time during clinic to explain study → very low recruitment
  - PCP not ‘engaged in research’, so need on-site study nurse to get informed consent → no ↓ cost
  - No reliable way to get PCP permission remotely
- With the Diuretic Comparison Project, we now present solutions to these problems

Diuretic Comparison Project
Study Question

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

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"Thiazide-like diuretics"

- Thiazide-like diuretics are first line therapy for HTN
- HCTZ: top 10 drugs in US, 135 million rx/yr
- In VA, >1 million veterans prescribed a thiazide-like diuretic each year: 95% HCTZ, 2.5% chlorthalidone
- Why HCTZ?: Merck, combinations, early VA trials, "HCTZ", claims of less hypokalemia (more later)
- The 2 drugs are used completely interchangeably
  - i.e. there is no pt characteristic that favors either drug
- But indirect evidence over past 35 yrs suggests CTD may be more effective at reducing CV outcomes

The beginning: MRFIT & chlorthalidone

- MRFIT: RCT of multi-component 'special intervention' vs usual care to prevent CV events
- Sites could use HCTZ or CTD (50 or 100 mg daily) as first-line Rx of HTN in special intervention arm
- CHD mortality of special intervention clinics using HCTZ was 44% higher than CTD clinics
- In 1980, MRFIT Policy Advisory Board changed protocol, recommending CTD over HCTZ for initial therapy, and lowered max dose to 50 mg
- After that, CHD mortality in the former HCTZ clinics ↓ by 28% (CTD or regression to the mean?)

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Since then, CTD has done well in RCTs

- No ‘CTD vs HCTZ’ RCTs for clinical outcomes
- Network meta-analysis – (assumes transitive property: if Vikings beat Packers and Packers beat Broncos, then Vikings will beat Broncos):
  - 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 (less anti-generic bias)?

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CTD vs. HCTZ – what's the difference?

- Studies show CTD has ≈2x the potency of HCTZ
- But CTD not used at lower doses (? savvy CTD users)
  - No RCT evidence that HCTZ 12.5mg is effective
  - JNC8 rec (Table 4): CTD 12.5-25mg, HCTZ 25-50mg
- CTD has longer elim. half-life (50-60 hrs vs 9-10 hrs)
  - lower BP with CTD during the nighttime hours
    (by 24-hr ambulatory BP monitoring)
  - nighttime BP is better predictor of CV outcomes than daytime BP
    (in large observational studies)
- One *in vitro* study of pleiotropic effects:
  CTD →↓ plt aggregation & ↑angiogenesis vs. a thiazide
  - No reports of related clinical effect (e.g., ↓ clotting)

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 …

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Shortly after our first planning meeting: a jolt of equipoise

Annals of Internal Medicine | ORIGINAL RESEARCH

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.

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Population-based observational study from Ontario (Dhalla, Ann Intern Med 2013;158:447)

- CTD (all 10,384 pts) vs. HCTZ (propensity-matched sample of 19,489 pts), mean f/u of about one year
- CTD used at higher doses (despite greater potency), and with less ACEI/ARB (↑K) (adjusted for these)
- CTD: NS↓ in MACE, 3.2 vs 3.4/100 pt-yr (adj HR 0.93, CI: **0.81**-1.06)
- CTD: ↑admissions "with" (not necessarily "for"):
  - ↓K (.69 vs .27/100 pt-yr, adj HR 3.06, CI: 2.04-4.58)
  - ↓Na (0.69 vs 0.49/100 pt-yr, adj HR 1.68, CI: 1.24-2.28)

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CTD still might be better

- 95% CI allow 19% decrease in MACE w CTD
- The rare CTD pts (& their MDs) could be quite different
  - Review of US data: CTD used in pts with more severe co-morbidities than HCTZ. Asche C. Value Health. 2013;16(3):A295.
- "a network meta-analysis must be considered observational evidence, but is arguably less prone to confounding bias than an observational comparative (prospective) cohort study". Jansen JP. ISPOR Task Force on Indirect Treatment Comparisons. Value Health 2011;14:417.

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DCP Study Design

1) Prospective randomized open-label blinded-endpoint (PROBE) trial.

2) Centralized informatics-based clinically integrated structure.

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Inclusion Criteria

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) ≥ 120 mm Hg, & no SBP < 120 mm Hg w/in 90 days before randomization (minimize risk, maximize benefit)

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Exclusion Criteria

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)

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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)

Rationale for open-label design

- blinded study drug could inhibit PCP management
- no local PI to assist with emergency unblinding
- open label is more familiar and straightforward to patients, may enhance recruitment
- ★ local pharmacy management of blinded drug would require ↑ effort & ? local “engagement in research”
- ★ $ of producing identical drugs, labeling and tracking

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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

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Why not all-cause mortality?

"If outcomes that are causally related to the trial treatment are combined with those that are not, the estimate of the treatment effect is diluted towards the null and we may fail to identify potentially important benefits or harms. …

Because few treatments will be causally related to all causes of death, ***all-cause mortality is a composite outcome*** that combines causally related causes of death with those unrelated to the treatment."

Prieto-Merino & Ian Roberts. Dangers of non-specific composite outcome measures in clinical trials. BMJ 2013;347:f6782.

Why non-cancer deaths?

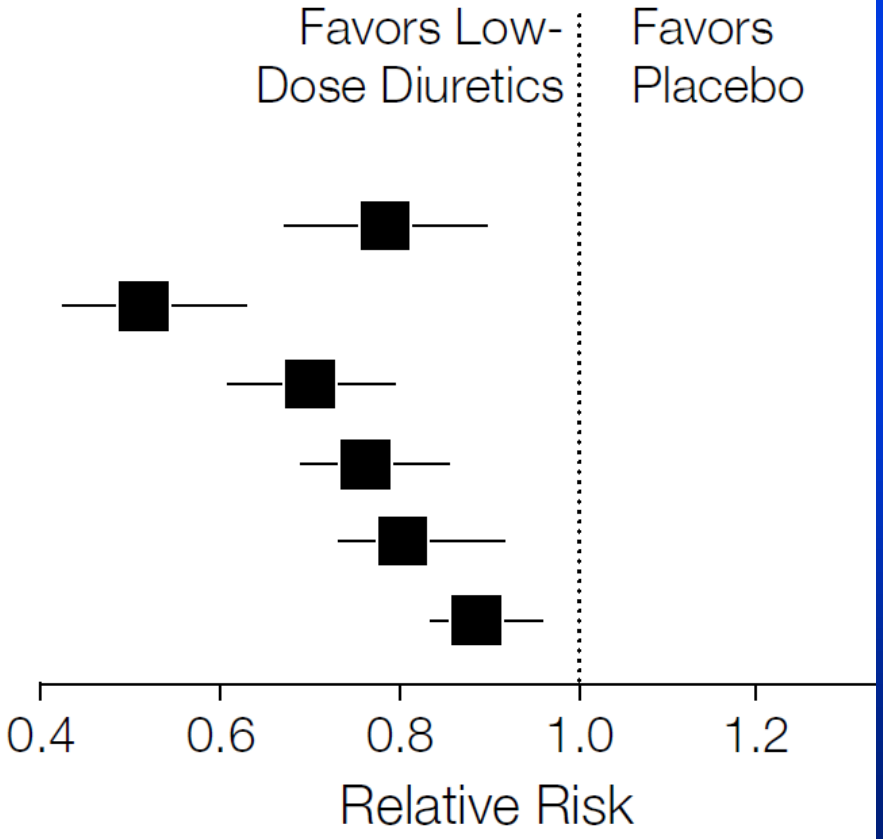
- We expect deaths to be ≈ 1/3 CV, 1/3 Ca, 1/3 other
- Some “other” deaths are relevant; i.e.,
  - accidents due to syncope from hypotension
  - deaths from unknown causes (?CV)
- “Other” deaths can be hard to distinguish from CV deaths (pneumonia & COPD can look like CHF)
- Cancer deaths are relatively accurate by death certificates, and believed unrelated to diuretic use
  - In PHS: Ca deaths identified from DC w >99% specificity (Sesso, Gaziano et al. Contemp Clin Trials 2006;27:333)
  - so excluded deaths should really be cancer

CHF is the outcomes most improved by diuretic rx of HTN

Figure 2. Network Meta-analysis of First-Line Treatment Strategies in Randomized Controlled Clinical Trials in Hypertension

A Low-Dose Diuretics vs Placebo

Outcome	RR (95% CI)	*P* Value
CHD	0.79 (0.69-0.92)	.002
CHF	0.51 (0.42-0.62)	<.001
Stroke	0.71 (0.63-0.81)	<.001
CVD Events	0.76 (0.69-0.83)	<.001
CVD Mortality	0.81 (0.73-0.92)	.001
Total Mortality	**0.90 (0.84-0.96)**	**.002**



Psaty BM. JAMA 2003;289:2534-44.

DCP: Secondary outcomes

- All deaths (follow-up continues after non-fatal event)
- “Possibly vascular deaths” - caused by vascular diseases, diabetes, external & unknown causes
- The composite outcomes substituting all deaths or “possibly vascular deaths” for non-cancer deaths
- Each component of the composite primary outcome
- Any revascularization of any artery
- Kidney stones

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DCP Process variables

From VA EMR:

- Blood pressure
- Compliance with study drug
- Use of other antihypertensive drugs

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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
- Acute gout episodes
- Erectile dysfunction
- New allergic reaction to thiazide-type diuretic

Outcome data collection

- Via EMR/administrative data: VA, CMS, SS, NDI
  - Expect half of all outcomes will occur outside VA
- Passive; no additional tests or procedures
- Outcome processing by investigators at MAVERIC, unaware of treatment group
- CMS records supplemented by VA references to event
- Review early & gray zone outcomes in VA EMR
- Now: chart review of VA admissions (non-study) to assess accuracy of relevant ICD codes

Hospitalization for acute CHF

- Reviewed 450 VA charts w 1° ICD 9 = “possibly CHF”
- 2 reviewers of VA EMR: “probably yes” or “probably no”
- Compute accuracy of different code combinations
- Excluded 398.91, 416.9, 425, 429.3, 514, some 402/4
- {402/4: .01,.11,.91, 415.0 , **428**, 518.4} > 90% accuracy
- Should apply to CMS records (maps to ICD 10)

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Sample Size

90% power to detect 17.5% relative reduction in CTD group, at 2-sided p = .05, assuming 3%/year occurrence of composite 1° outcome in HCTZ group (from literature, esp. Ontario) with mean f/u of 3 yrs → total n = **13,500** pts

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Putting that in perspective

- 13,500 pts = 1.44 x SPRINT
- SPRINT: 1660 in VA (for > $21 million)
- Most VA pts ever in a HTN trial:
  7000 in ALLHAT
- We can't do this the old way

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Proposal for an inexpensive large VA RCT ("point of care" or "clinically integrated")

1) find eligible patients using VA EMR
2) centralized recruitment and enrollment
3) centralized placement of notes & orders in VA EMR
4) PCPs: permission & pt care (including study drug)
5) centralized collection of outcomes from databases
6) no employed local personnel
7) sites not "engaged in research"

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Informing local VA personnel

- No local IRB or R&D review
- Conference call w leadership
- Preparatory work with pharmacy, IT staff
- MAVERIC sends info letter & email to PCPs
- Site Liaison: MD (1° care or HTN) at each site
  - not ‘engaged in research’ (no credentialing)
  - local source of information
  - help prepare site with: pharmacy, IT staff
  - address staff meetings, give conferences, grand rounds, etc.

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The PCP and study recruitment

- An opportunity to participate in a major study relevant to their practice with minimal effort
- PCP's will be sent a 'test-patient order' re: contacting their pts, to sign ("yes") or discontinue ("no")
- "yes" also means PCP agrees to be a study subject
- "Contact" = letter with study information and the opportunity for the patient to opt out
- Sent from MAVERIC to eligible pts of willing PCPs

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Enrollment & management

- Consent obtained by central phone bank at VA in Canandaigua, NY (**key** feature, & not ‘point of care’!)
- PCP gets view alert order to approve randomization of each pt, to sign (“yes”) or discontinue (“no”)
- Randomize: now pt is in, intent-to-treat
- PCP manages dose, monitoring, dc, etc, as usual
- We will query PCP if diuretic discontinued or expired

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Voilà - our 3 problems are solved

1) Central telephone consent means no on-site study nurse (requires a waiver, discussed later)
2) We do not ask provider to take extra time during clinic – just respond to view alerts in admin time
3) 'Sign or discontinue' view alert order provides reliable way to get provider permission remotely

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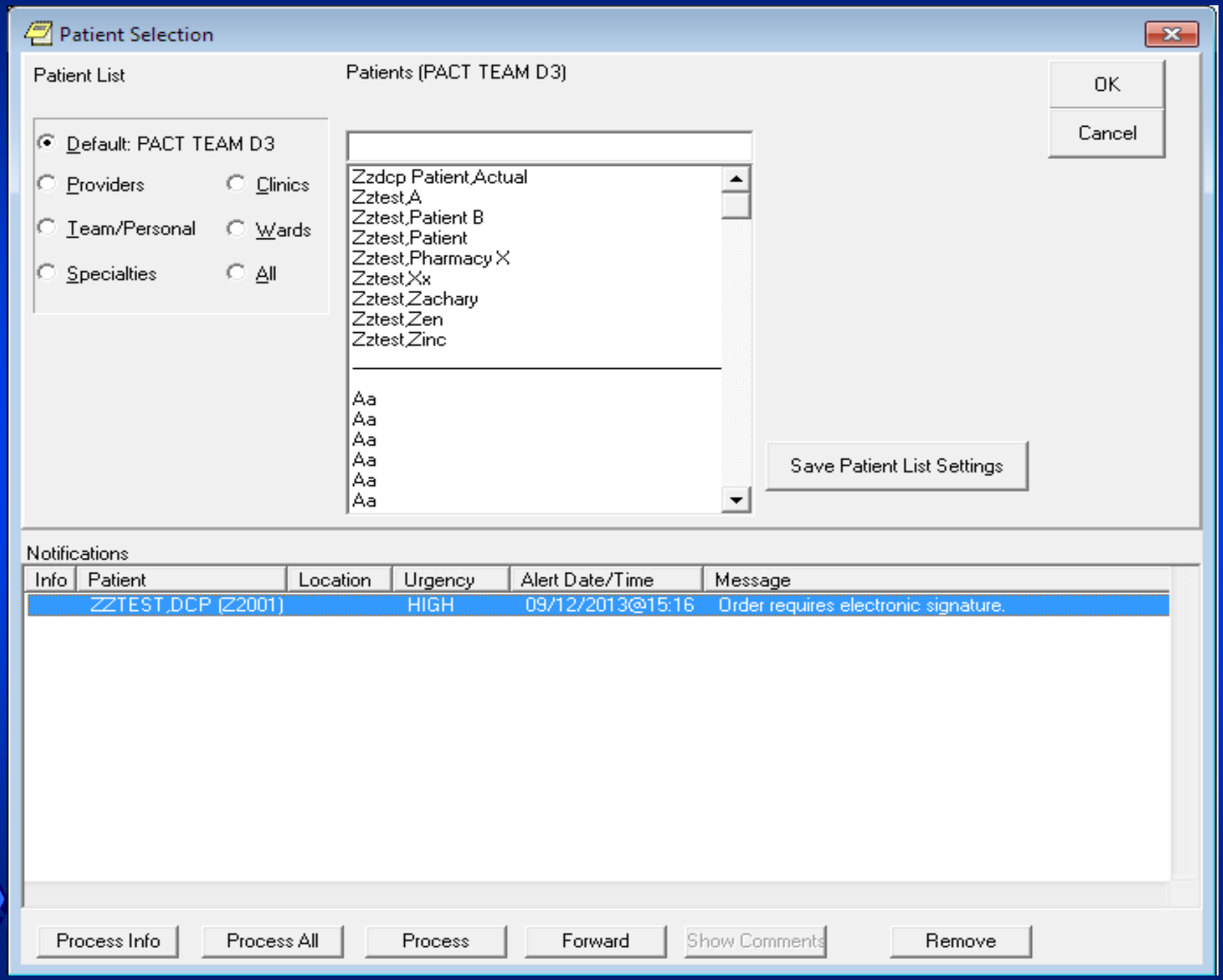
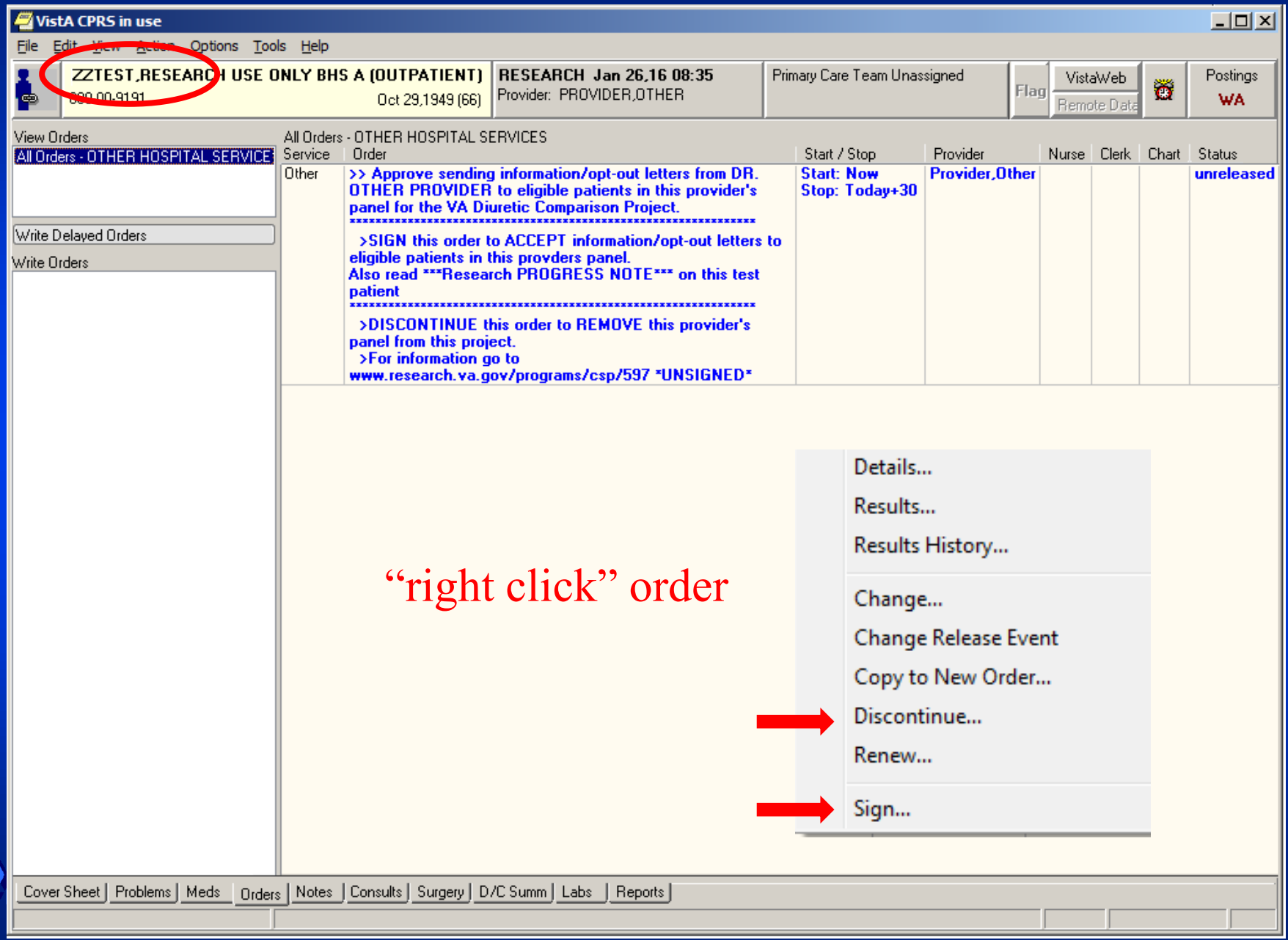
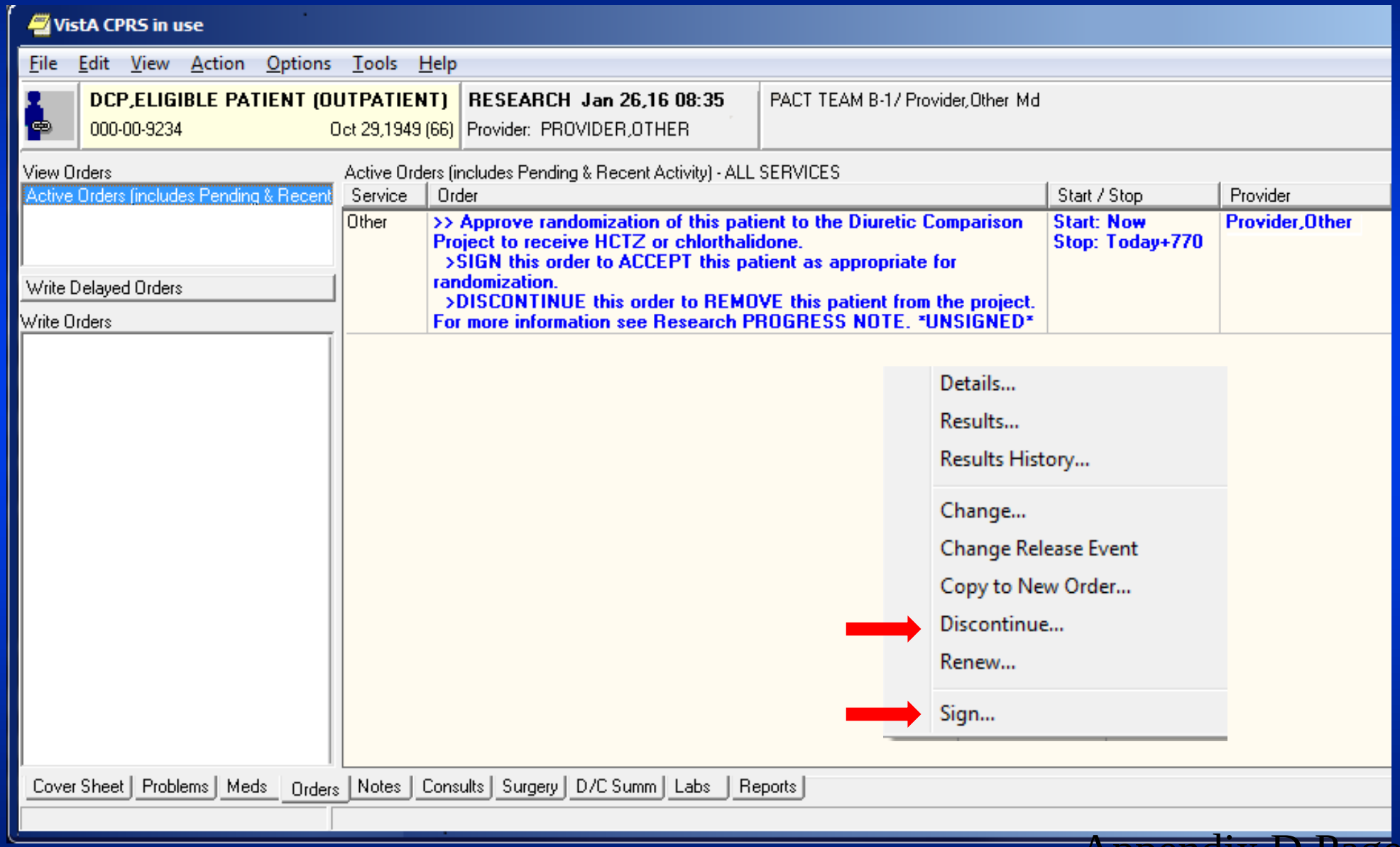
View Alert for Approval to Recruit Patients in PCP's Panel



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



After patient consents: PCP approval to randomize



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

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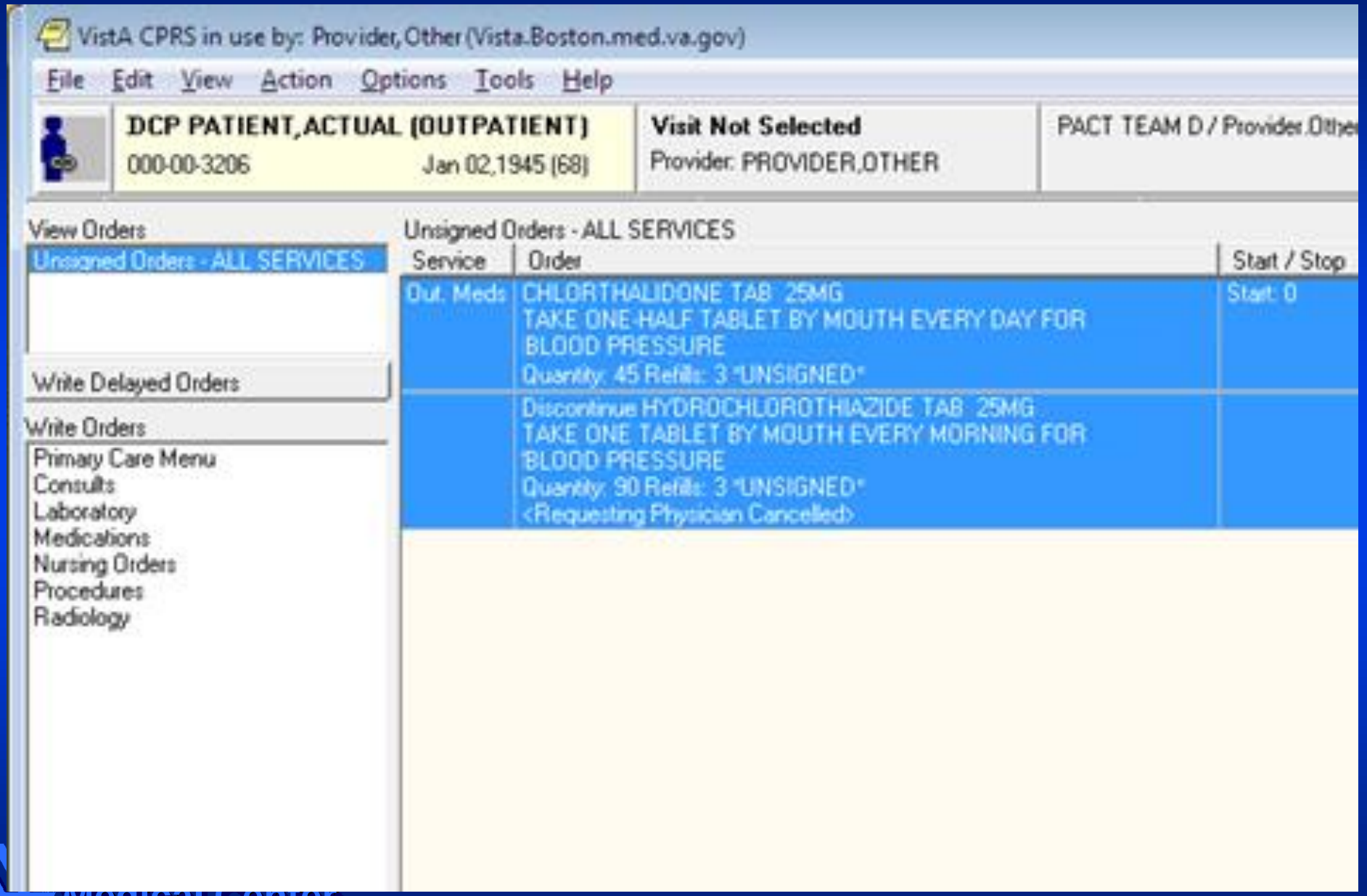
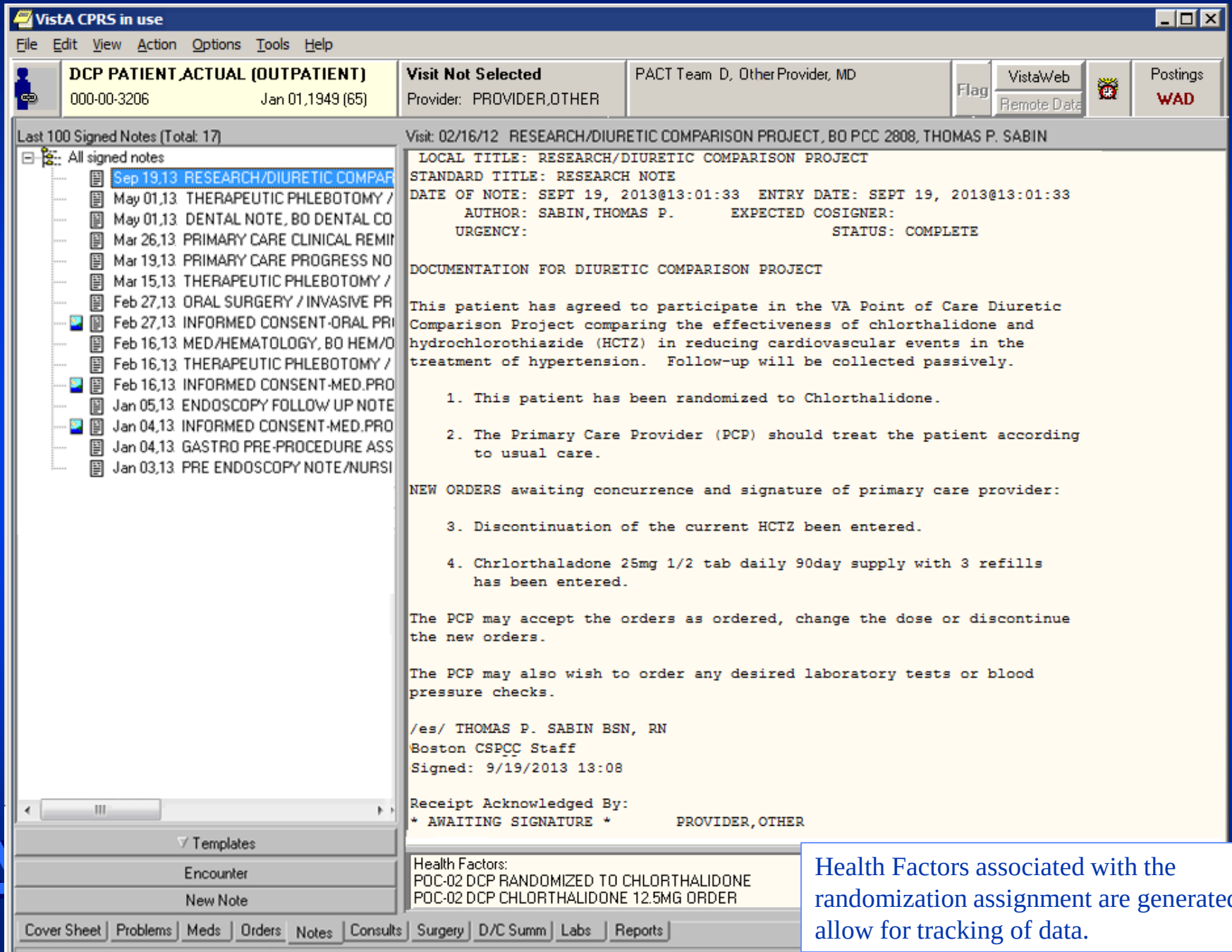
Randomization Orders



Randomization Note



Health Factors associated with the randomization assignment are generated and allow for tracking of data.

Feasibility 1

- From VA database: # pts over 65 prescribed single-agent HCTZ 25 or 50 mg, per VA per yr
- In NE region, 80% of these had SBP ≥120 mm Hg at last check w no SBP <120 mm Hg w/i 90d
- Apply that 80% nationally→
  104 VAMC's with ≥1000-3900 eligible pts
- N = 13,500 pts = 270 per site at 50 sites
- We need ≈10% of all eligible pts at the 50 sites

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Feasibility 2

- Based on other VA studies & early data, we estimate:
  - 15% of PCPs will opt out
  - 30% of pts mailed the initial letter will opt out
  - We will reach 65% of pts we attempt to call
  - 25% of remainder will agree
  - 2% of those who agree will be removed by PCP
- Combining: (.8)(.7)(.65)(.25)(.98) ≈ 9.5% of eligible pts. May need 50-70 (of 168) VA medical centers.

Timeline

- 3 yr enrollment + 1.5 yr f/u = 4.5 yrs
- 0.5-1.5 more yrs to get CMS records
- Total = **5-6 yrs**
- We must enroll 100/wk, call 654/wk, for 3 yrs

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Why hasn’t this been done before?

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Even the friendliest IRB must obey The Law (Common Rule)

VHA HANDBOOK 1200.05

- IRB-approved informed consent form that includes all the required elements and, as appropriate, additional elements
- Informed consent form must be signed & dated by:

  (1) The subject or the subject's representative,

  (2) The person obtaining the informed consent, and

  (3) A witness, if required by IRB. A witness is always required when a short form consent is employed.

This is hard to do remotely!

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REQUIREMENTS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH

34. WAIVER OF DOCUMENTATION OF INFORMED CONSENT

a. **Criteria for Waiver.** The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds and documents either (38 CFR 16.117(c)):

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern (38 CFR 16.117(c)(1)); or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (38 CFR 16.117(c)(2)).

35. WAIVER OF INFORMED CONSENT — VHA HANDBOOK 1200.05

b. **Minimal Risk Research.** The IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or the IRB may waive the requirements to obtain informed consent, provided the IRB finds and documents that (38 CFR 16.116(d)):

(1) The research involves no more than minimal risk to the subjects (38 CFR 16.116(d)(1));

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects (38 CFR 16.116(d)(2));

(3) The research could not practicably be carried out without the waiver or alteration (38 CFR 16.116(d)(3)); and

(4) Whenever appropriate, the subjects are provided with additional pertinent information after participation (38 CFR 16.116(d)(4)).

What is meant by "minimal" or "practicably"?

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VHA HANDBOOK 1200.05

vv. **Minimal Risk.** Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (38 CFR 16.102(i)).

But we know of no prior randomized drug trials being ruled 'minimal risk'

HHS.gov
U.S. Department of Health & Human Services

When may the requirement for documentation of informed consent or parental permission be waived or altered?

When an Institutional Review Board (IRB) has not waived the requirement for seeking prospective informed consent of the subjects or the parental permission of children who are subjects, under the HHS regulations at 45 CFR 46.117(c), it may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

1. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern; or
2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., drawing a blood sample, or asking shoppers in a mall about the ambient lighting or temperature).

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Conditions requested from VA Central IRB

- Waiver of HIPAA Authorization (to identify and contact eligible patients)
- Waiver of Documentation of Informed Consent on the basis of minimal risk (to obtain consent by phone without signed copy)
- Local VA's (& PCPs) not 'engaged in research'

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Why not ask for a full Waiver of Informed Consent?

- This is an FDA-regulated study and FDA doesn't have this provision ('uncommon' part of Common Rule)

- Risk of fatal Washington Post headline: "VA enrolling veterans in drug trial without their consent"

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Why not have signed consent mailed back?

Experience shows that requiring mailed-back written consent eliminates ***most*** patients who would consent:

- In Seattle VA phone surveys, 97% agreed to it, but where returned form required, only 43% did
  Nelson, Med Care 2002;40:283-8.
- In Harvard study, 93% consented with letter followed by phone call, but only 26% if returned form required
  Cann, IRB 1984;6(4):5-7.
- Consent for U Mich registry dropped from 96.4% w phone to 34.0% w returned form. When later amended to an opt-out letter, only 5% opted out
  Armstrong, Arch Intern Med 2005;165:1125-9. Kaiser, Science 2006;311:1547-8.

“mail it back” continued

- RAND sent opt-out consent to 117 parents re: enrolling kids in an educational program.
  Ellickson, Eval Rev 1989;13:45-55.
  - 4 opted out, reached 94 of remaining 113 by phone, 90 of 94 gave permission.
  - Concluded “equating nonresponse with permission accurately reflected the wishes of 96% of the parents reached by phone”.
- So most pts will agree (passively), few will mail back.

If requirement of returned written consent eliminated most eligible patients from our study, it is unlikely that it could be done within the VA = not “practicable”

‘Engagement’ in Research

- Engaged site needs SAE review, site visits, etc
  - Probably need local personnel for this
- We argued only MAVERIC (Boston), Chair’s VA’s, & call center VA are ‘engaged’
- We argued site Liaison & PCP’s NOT engaged in research (would need research training).
- The site Liaison only provides information to local site personnel about the study
- The PCPs are study subjects - we are studying how effectively they implement the protocol.

Correspondence

VA Central IRB
VA Institutional Review Board for Multisite Studies

FROM: VA Central IRB

DATE: January 4, 2016

TO: Frank A. Lederle, MD
Minneapolis VA Medical Center

William C. Cushman, MD
Memphis VA Medical Center

SUBJECT: Final Review by the VA Central IRB of
Project Application, VA Central IRB #1

1. The response to the additional minor modification
convened meeting on November 20, 2015, for the
expedited review procedures and all required mod
made.

Project Title: CSP 597: Diuretic Comparison

Date of Response: December 21, 2015

2. The PI/SC New Project Application is now **Approved**. All criteria for IRB approval have been met. The following determinations were made regarding this project:

   - The project is no more than minimal risk to participants and the risk is reasonable in relation to anticipated benefits.
   - The continuing review period is one year with an expiration date of **November 19, 2016**.

3. The VA Central IRB also made the following additional determinations:

   - **Waiver of the Informed Consent Process is approved for recruitment purposes only** as described in VA Central IRB Form 112a. All approval criteria for this waiver have been met.
   - **Waiver of Documentation of Informed Consent is approved** for both providers and veteran participants as described in the VA Central IRB Form 112b. All approval criteria for this waiver have been met.
   - **Waiver of HIPAA Authorization is approved** for veteran participants as described in VA Central IRB Form 103. All approval criteria for this waiver have been met.
   - The use of SSNs was approved in order to collect data from VA and CMS databases and to access veteran research subjects' electronic medical records.

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The large inexpensive RCT

- SPRINT (n=9361): > $150 million
  - > $15,000/pt
- DCP (n=13,500): < $10 million
  - < $750/pt
- <1/20: < 5¢ on the $

ADAPTABLE (1st NIH PCORnet trial): $930/pt

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Why DCP was the right question

- Minimal risk – starting a thiazide is low risk, changing thiazides is minimal risk
- Pt's needs are not subordinated to needs of trial
  - No patient characteristic favors either drug
  - PCP manages the drug as usual
- Minimal risk ≠ minimal value
  - potential benefit is large enough to merit funding
- Equipoise – Ontario observational study
- Enough eligible patients to benefit from the design

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DCP update

August, 2016 - First pt randomized at Boston VA

Study now on hold while we revise invitation materials in effort to increase acceptance rate

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MAVERIC DCP Team

- Mary Brophy
- Kelly Cho
- Ryan Ferguson
- Lou Fiore
- Amanda Guski
- John Hermos
- Jim Kaufman
- Vick Kudesia
- Bob Lew
- Jade Riotto
- Tom Sabin
- Patricia Woods

VACO Team

Terri Gleason, Karen Jeans, Eric Schwinder

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