THE DARTMOUTH INSTITUTE
FOR HEALTH POLICY & CLINICAL PRACTICE

Clinical Trials

Jon D. Lurie, MD, MS

TREAT
CENTER FOR TRANSLATION OF REHABILITATION ENGINEERING AND ADVANCES AND TECHNOLOGY

Dartmouth-Hitchcock
MEDICAL CENTER

GEISEL SCHOOL OF MEDICINE AT DARTMOUTH

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"*You* gotta be careful *if you don't know where you're going*, otherwise *you* might not get there".

Yogi Berra

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Validity

Internal Validity – the answer you think you got is the RIGHT answer in this population.

External Validity – the answer you got in the members of the population studied is the SAME answer that would have been obtained in the REST of that population.

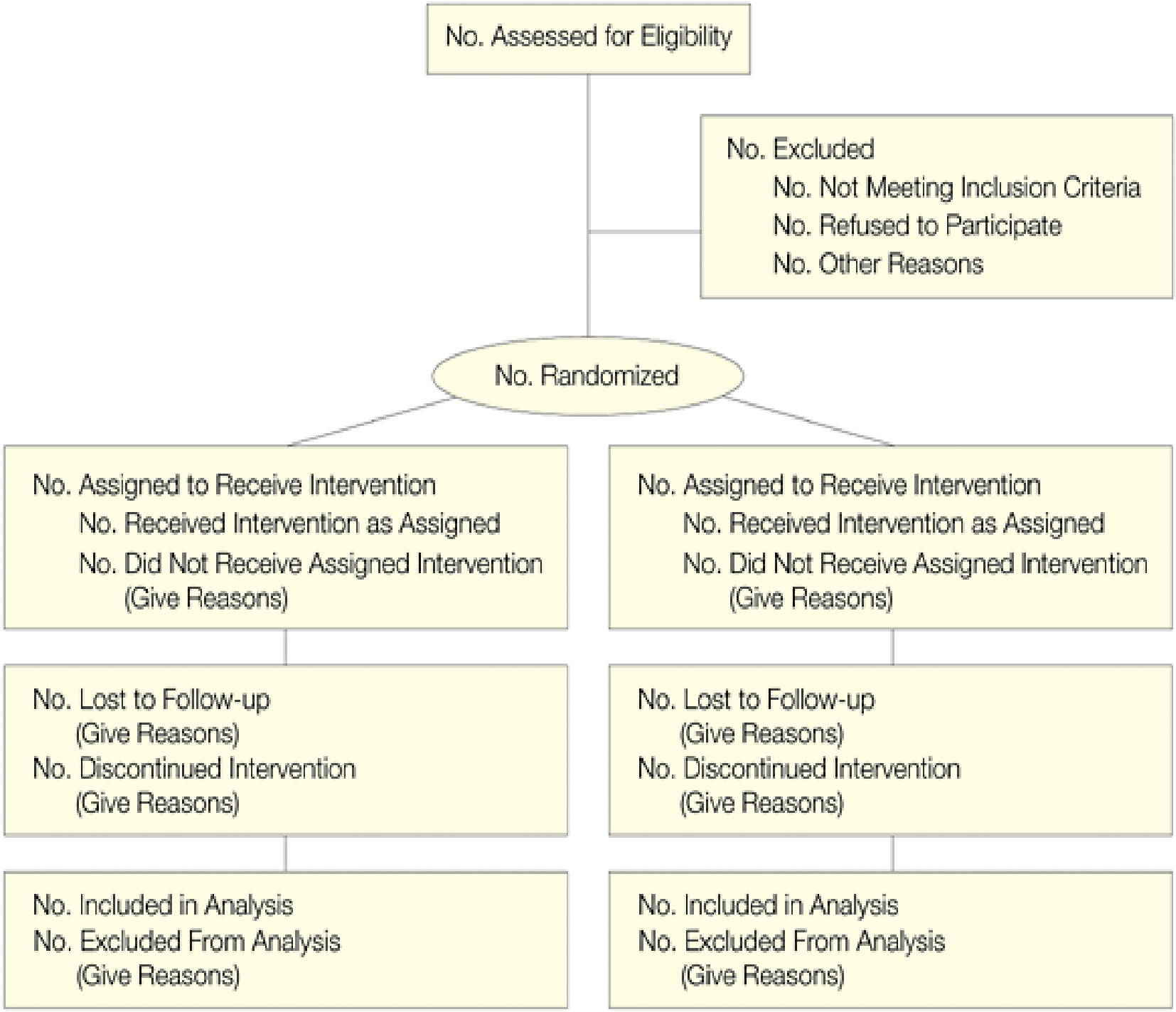
"Perfectly Valid" Study

- Completely homogeneous groups
- Completely identical environments
- Everything same except for the intervention
- Intervention identical in all subjects
- 100% follow-up
- Completely objective and reliable outcomes
- Data collection completely uniform

“Perfectly Valid” Study

- Possible with inbred mouse strains
- Close to it in short term physiology studies
- Rough approximation in critically ill patients

- Forget about it in long-term studies of free-range humans


No. Assessed for Eligibility
No. Excluded
No. Not Meeting Inclusion Criteria
No. Refused to Participate
No. Other Reasons
No. Randomized
No. Assigned to Receive Intervention
No. Received Intervention as Assigned
No. Did Not Receive Assigned Intervention
(Give Reasons)
No. Assigned to Receive Intervention
No. Received Intervention as Assigned
No. Did Not Receive Assigned Intervention
(Give Reasons)
No. Lost to Follow-up
(Give Reasons)
No. Discontinued Intervention
(Give Reasons)
No. Lost to Follow-up
(Give Reasons)
No. Discontinued Intervention
(Give Reasons)
No. Included in Analysis
No. Excluded From Analysis
(Give Reasons)
No. Included in Analysis
No. Excluded From Analysis
(Give Reasons)

Major Internal Validity Threats

- Unequal Groups at Baseline
  - Selection Bias
- Unequal Groups at Follow-up
  - Drop-outs
  - Exclusions
- Unequal Treatment
  - Non-adherence
  - Cointerventions
  - Unequal outcomes assessment

Unequal Groups at Baseline

Two steps to prevent selection bias:

- Randomization
- Allocation Concealment
  - Treatment unknown until enrolled and assigned

Unequal Groups at Baseline

Keys to proper Randomization:

- Only random is random
  - Arbitrary assignment is unacceptable
    - Even/odd ID#, days of week,
- Subversion of randomization happens!

Unequal Groups at Baseline

Subversion of Randomization:

- Steaming open sealed envelopes
- “Hot Lighting” envelopes
- Opening multiple envelopes until “desired” assignment
- Multiple calls to central number for allocation and then “distributing” assignments
- Breaking in to the PIs office

Schulz KF. JAMA 1995 274:456-58

Unequal Groups at Baseline

Does Allocation Concealment Matter?

YES!! Studies with inadequate or unclear allocation concealment on average show larger effects estimates than those with adequate concealment – 41% and 33%

(compared to 19% for inadequate blinding)

Unequal Groups at Baseline

Take Home Point for Researchers:

Allocation concealment must be deliberate, fool-proof, and clever-proof.

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Unequal Groups at Follow-up

- Drop-outs are typically non-random
  - Direction of bias can be unpredictable
- Placebos/blinding originally introduced in this country to address this issue

- Follow-up is MORE IMPORTANT than enrollment

Unequal Groups at Follow-up

- Study A – projected sample size 200, enrolls 100, follows up100%
  - Valid, though underpowered study

- Study B – projected sample size 200, enrolls 200, follows up 50%
  - Equally underpowered AND invalid

Unequal Groups at Follow-up

Take Home Point for Researchers:

No matter what the PI says, no matter what the funding agency says, no matter what the financial incentives are –

Follow-up is MORE important than enrollment!

Unequal Groups at Follow-up

Exclusions must be independent of post-randomization events

- Ineligibles discovered after enrollment by routine (evenly applied) procedures can generally be excluded, those discovered as a direct or indirect consequence of the treatment should not be.

Confounding

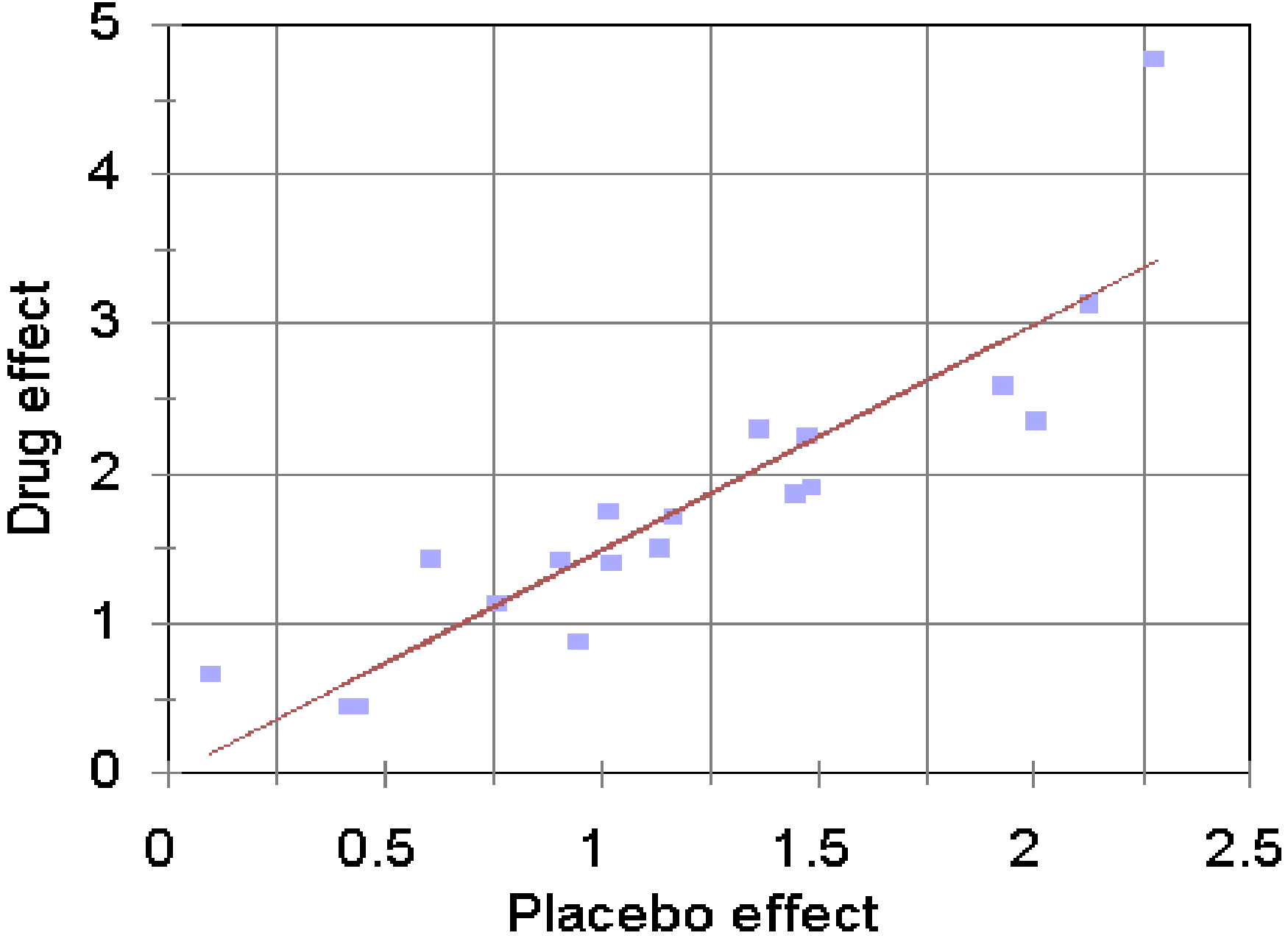
Is Clofibrate Life-Saving?

Compliance	5-year mortality
< 80%	24.6%
≥ 80%	15.0%

Confounding

Is Clofibrate Life-Saving?

	5-year mortality	
Compliance	**Clofibrate**	**Placebo**
< 80%	**24.6%**	**28.2%**
≥ 80%	**15.0%**	**15.1%**


Drug effect
5
4
3
2
1
0
0
0.5
1
1.5
2
2.5
Placebo effect

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Unequal Treatment

Non-adherence

- Cross-over in unblinded trials
- Not taking pills, attending sessions, etc.
- Faking it – e.g. dumping
- Bogus participation

Non-adherence

DUMPING – The Lung Health Study

- Study of regular bronchodilator use in COPD
- MDI recorded time and date of each use
- 30% actuated MDI > 100 times in < 3h
  - Usually right before a study visit
- No patient characteristics were predictive of dumpers vs non-dumpers

Chest. 2000 Aug;118(2):290-5

Non-adherence

Bogus Participation – perils of IVRSs

- RCT of 2 barrier contraceptives
- Enrolled by phone - $150 remuneration
- Of 1st 25 participants – 31% suspicious
  - 4 used same phone for each survey minutes apart
  - 2 others provided bogus addresses
  - These and 2 others withdrew when staff attempted to contact

JAMA. 2001 Jan;285(3):293.

Non-adherence

- Adherence is an important and difficult issue in trial
- May be in conflict with enrollment pressures
- May have informed consent implications

Co-interventions

- What are the rates of additional treatments in the two groups and are they different?

- Blinding/Placebos can be critical
- Not measured as often as it should be

Unequal Assessment

- Patient initiated
  - Recall bias
- Investigator initiated
  - Work-up bias

- Blinding can be critical

Unequal Treatment

Take Home Points for Researchers:

- Blind whomever and whenever possible
- Measure compliance BUT asking about compliance is like asking how much alcohol someone drinks

External Validity

- NO study is “Generalizable” but some studies are more generalizable than others
- i.e. Generalizable to WHOM or to WHAT
- Internal and External Validity may trade off against each other (efficacy vs effectiveness)

External Validity / Generalizability

Key Factors:

- Sample size – how big?
- Selection Criteria – how strict?
- Treatment Regimen – how realistic?
- Compliance – how realistic?
- Treatment Setting – self-selection?
- Study Setting – self-selection?

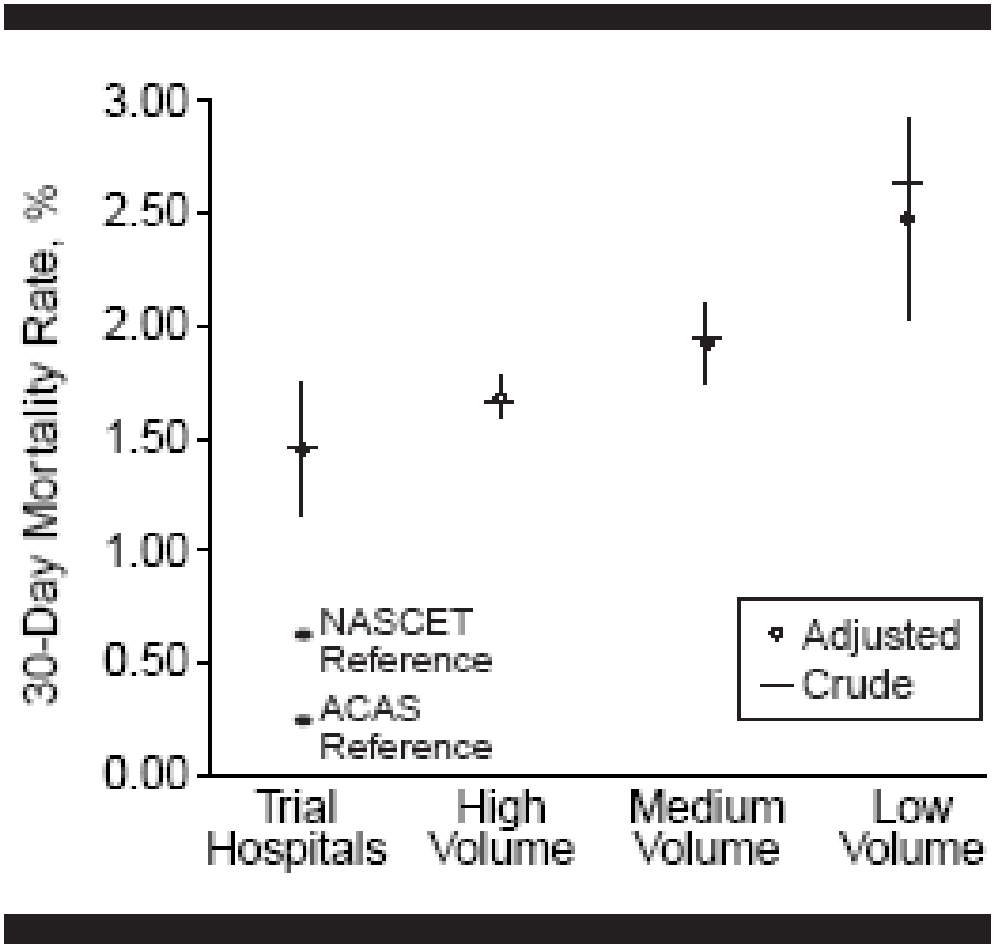
CEA Trials

Table I. NASCET and ACAS exclusion criteria

Criteria	*NASCET exclusions*	*ACAS exclusions*
Age (y)	>79	<40 or >79
Symptoms	Asymptomatic, ipsilateral >120 days before CEA	Ipsilateral symptoms or VBI, or contralateral symptoms within 45 days of CEA
	History of FMD, tumor, AVM, etc, that could cause symptoms	History of FMD, tumor, AVM, etc, that could cause symptoms, seizure disorder or migraines
	Stroke in evolution	Stroke in evolution
	Previous CVA with profound deficit, either side	Previous CVA with profound deficit, either side
Lesion	<30% or occluded	<60% or occluded (by ACAS)
	Tandem lesion > target stenosis	Tandem lesion > target stenosis
	Unsuitable for CEA	Unsuitable for CEA
Surgical Hx	Previous ipsilateral CEA	Previous ipsilateral CEA
	Previous contralateral CEA within 4 months	No exclusion
	Major surgery within 1 month	Major surgery within 1 month
Comorbidities	Kidney failure	Kidney failure (creatinine >3)
	Lung failure	Lung failure (impact 5-y survival)
	Liver failure	Liver failure
	Cancer, <50% 5-y survival	Cancer, <50% 5-y survival
	Atrial fibrillation	Atrial fibrillation
	Valvular heart disease	Valvular heart disease (including valve replacement)
	Uncontrolled DM	Uncontrolled DM (fasting glucose >400 mg/dL)
	Uncontrolled HTN	Uncontrolled HTN (>180 systolic, 115 diastolic, ×3)
	Unstable angina	Unstable angina
	MI within 6 months	No exclusion
	Symptomatic CHF	Symptomatic CHF
	No exclusion	Radiation treatment to neck
	No exclusion	Active ulcer disease
Allergies	Aspirin	Aspirin
	No exclusion	Coumadin use

VBI, Vertebrobasilar insufficiency; *FMD*, fibromuscular dysplasia; *AVM*, arterial venous malformation; *ACAS*, Asymptomatic Carotid Atherosclerosis Study; *DM*, diabetes mellitus; *HTN*, hypertension; *MI*, myocardial infarction; *CHF*, congestive heart failure.

CEA in Medicare



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CEA Registry

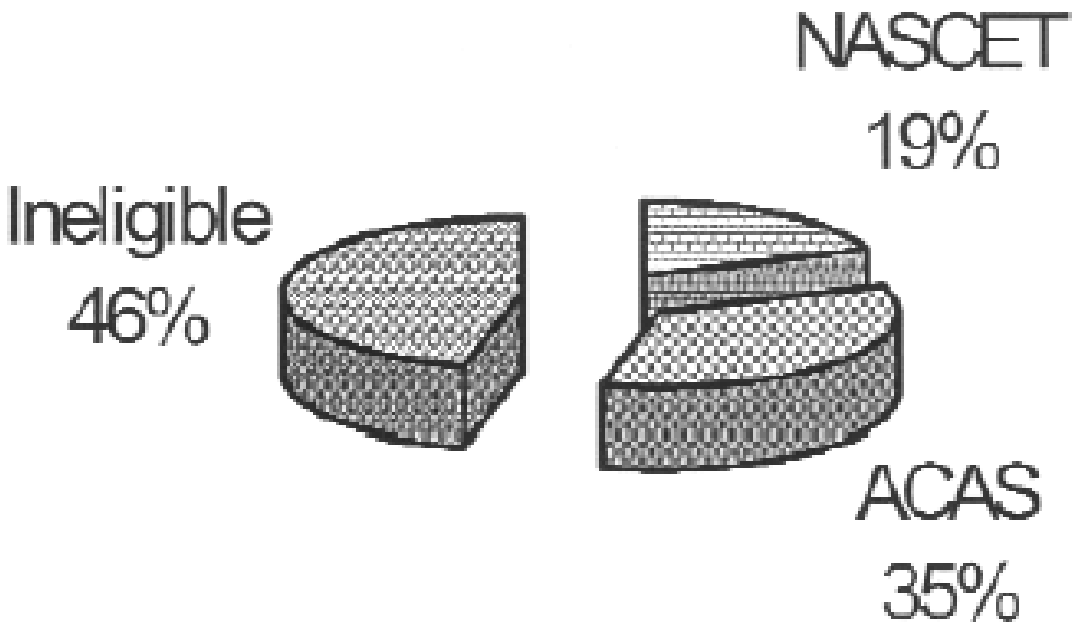

Fig 2. Breakdown of patient sample based on trial eligibility (N = 366).

CEA Registry

Table V. Neurologic events/trial eligibility

Carotid disease	*Eligible patients (CVA)*	*Ineligible patients (CVA)*	P *value*
Symptomatic (NASCET)	1.4% (1/70)	4.4% (3/68)	.3
Asymptomatic (ACAS)	1.6% (2/127)	3.0% (3/101)	.39
Total	1.5% (3/197)	3.6% (6/169)	.17

NB. NASCET n= 659; ACAS n= 1659

Comparative Effectiveness

"rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments, such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy."

Pragmatic RCT

- Select clinically relevant interventions to compare
- Include a diverse population of study participants
- Recruit participants from a variety of practice settings
- Collect data on a broad range of health outcomes.

Caveat Lector

When I read about the evils of drinking, I gave up reading.

Paul Hornung

U.S. Department of Health and Human Services

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P60-AR048094-01A1
K23 AR 48138-03

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NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases

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Spine Patients Outcomes Research Trial

Making wise choices...

TREAT Center for Translation of Rehabilitation Engineering Advances and Technology

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WHERE KNOWLEDGE INFORMS CHANGE

Geisel School of Medicine at Dartmouth

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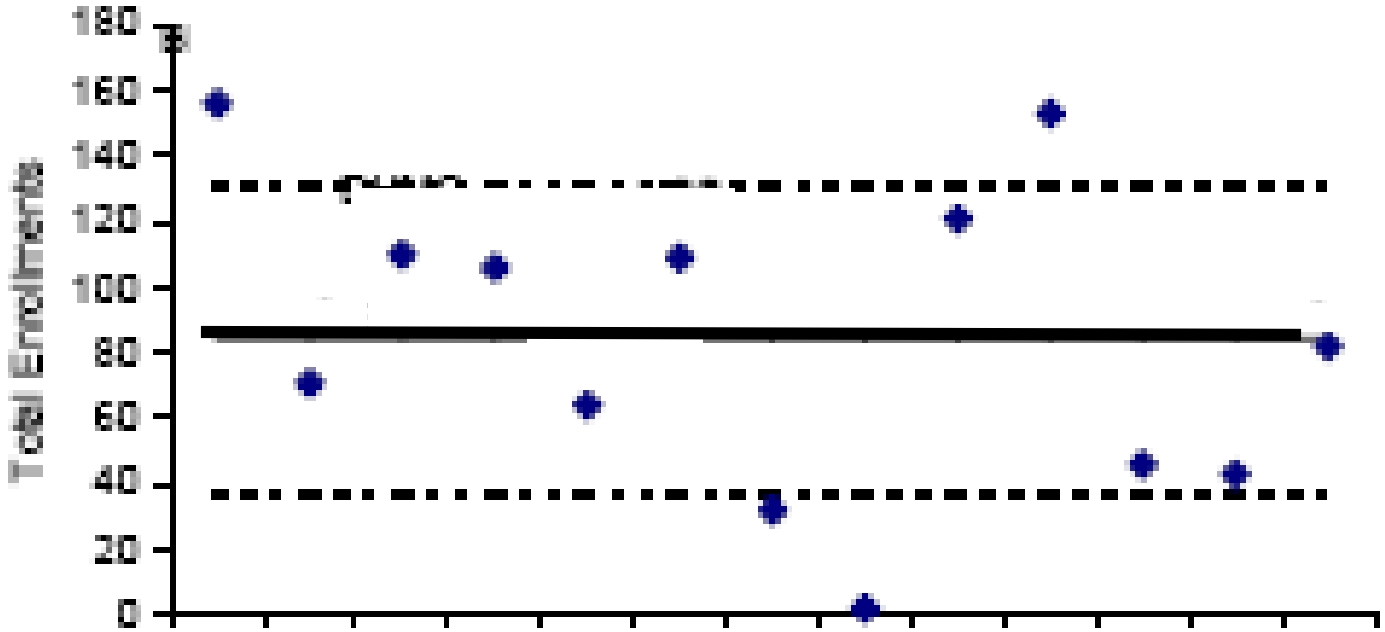
RCT Enrollments by Center- Totals to Date*



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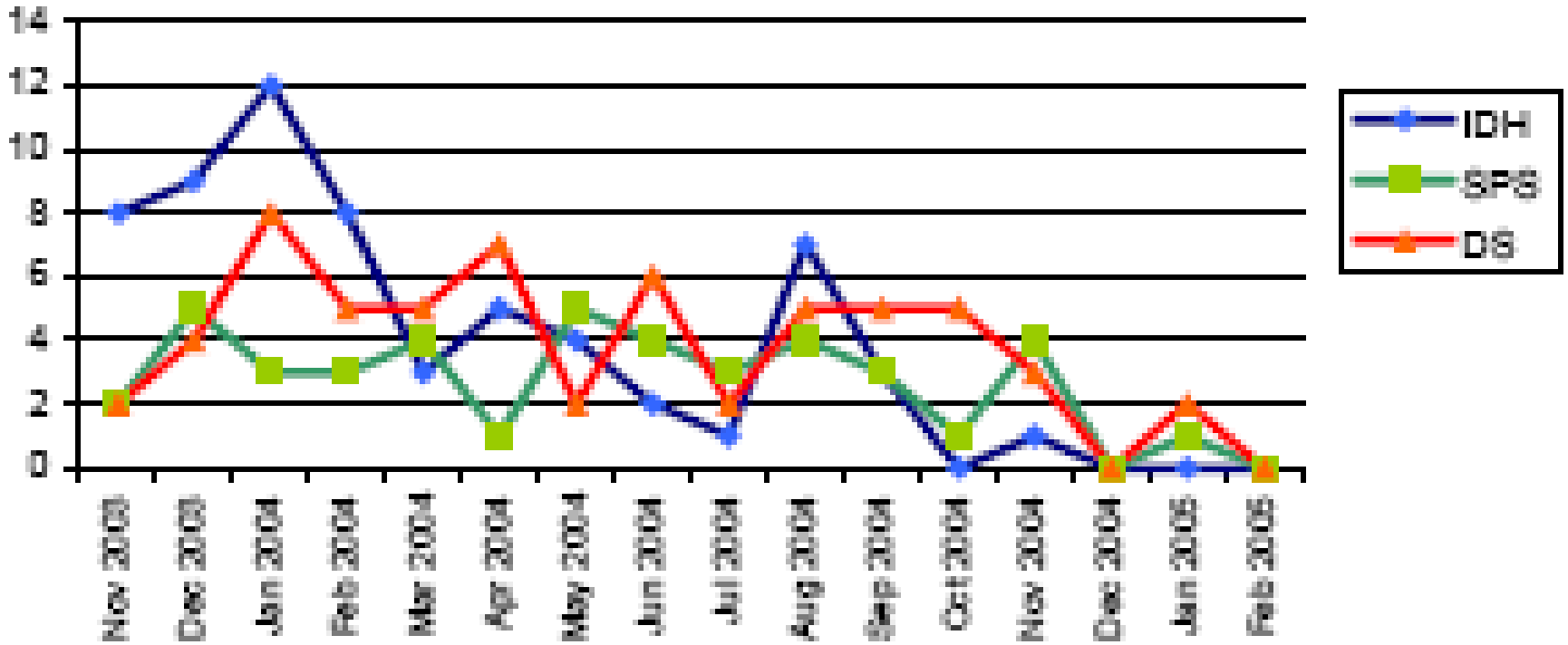
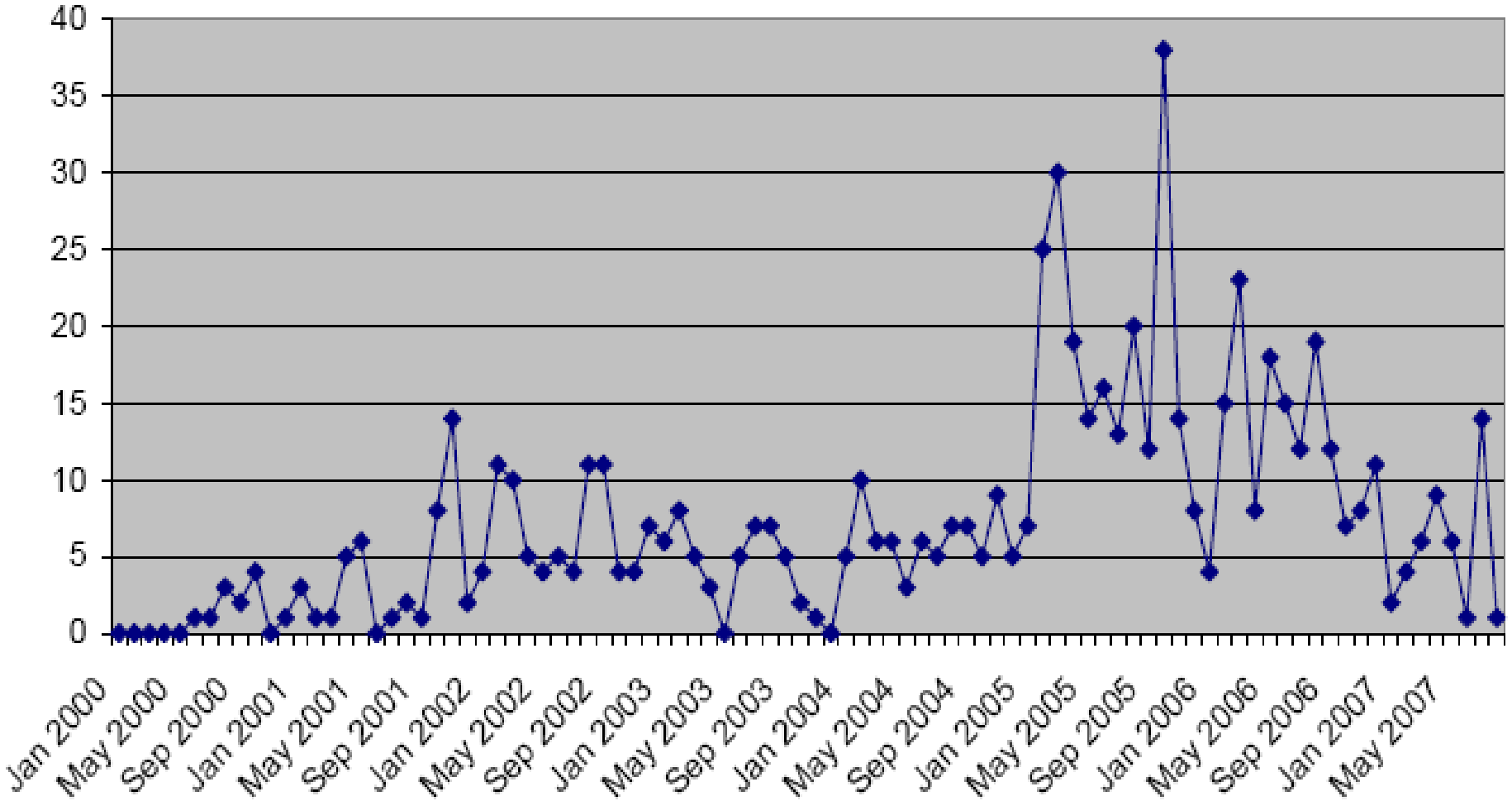
Monthly RCT Enrollments - All Centers



SPORT Withdrawals per Month



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