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Speaker

Second Plenary Session

WHAT ARE THE ADVANTAGES AND DISADVANTAGES OF USING OBSERVATIONAL DATA AS THE BASIS OF DECISION MAKING IN HEALTH CARE? HOW COULD THIS AFFECT THE FUTURE OF RANDOMIZED CONTROLLED TRIALS?



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Is it time to retire the RCT?

D.L. Sackett
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- a useful perspective?

*Why did folks like me
start doing RCTs
50 years ago?*

Conflicts of interest

Dave Sackett has been wined, dined, supported, transported, and paid to speak by countless pharmaceutical firms for over 50 years, beginning with two research fellowships and interest-free loans that allowed him to stay to finish medical school. Dozens of his randomised trials have been supported in part (but never in whole) by pharmaceutical firms, who never received or analysed primary data and never had veto power over any reports, presentations, or publications of the results. He has twice worked as a paid consultant to advise pharmaceutical firms whether their products caused lethal side-effects; on both occasions he told them “yes.” He has testified as an unpaid expert witness for a stroke victim who successfully sued a manufacturer of oral contraceptives, and as a paid expert in preparing individual suits against manufacturers of female hormones and NSAIDs and in a class-action suit against a manufacturer of prosthetic heart valves. He was paid by a pharmaceutical firm to develop “levels of evidence” for determining the causation of adverse drug reactions. His wife inherited and sold stock in a pharmaceutical company. While head of a division of medicine he enforced the banning of drug-detail personnel from clinical teaching units (despite the threat of withdrawal of drug industry funding for resident research projects). He received the Pharmaceutical Manufacturers’ Association of Canada Medal of Honour (and cash) for “Contributions to Medical Science in Canada” for the decade 1984-94. His most recent award (the 2010 Gairdner-Wightman Award) was sponsored by the Canadian Government and 21 research bodies, provinces, and manufacturers.

I began as a 1960s Intern-in-Trouble with my ‘expert’ Attending Physicians

1. For starting AHT drugs on a 26 Y/o asymptomatic man with sustained BP \geq 260/130.

 **Don't you know you will cause him to suffer a stroke ? !**

I began as a 1960s Intern-in-Trouble with my 'expert' Attending Physicians

2. For letting a post-MI patient get out of bed only 3 weeks after his mild heart attack.

💡 **Don't you know you will cause him to rupture his ventricle ? !**

The basis of these Expert Opinions

- 👁 Millions of brilliant clinical observations
- 👁 by brilliant clinicians
- 👁 of the clinical course and outcomes
- 👁 of millions of patients
- 👁 receiving thousands of treatments.

Why were Interns like me in trouble?

- ✖ We reckoned there were at least 4 things wrong with . . .
- ✖ . . . the way clinicians were using their clinical observations in those days . . .
- ✖ . . . to decide whether a treatment did more good than harm.

We were worried that mere observations of interventions and outcomes would prevent us from making:

‘Fair comparisons’

between different treatments;

including no treatment at all!

By “fair comparisons” we meant:

- ✓ the achievement and maintenance of equality
- ✓ between treated and comparison patients
- ✓ for all determinants of their outcomes
- ✓ except for their treatments.

What were our worries

1. We worried that docs might preferentially treat patients with better prognoses.

- In the 1930's, hundreds of thousands of NYC families contained one or more members with TB.
- Every year, thousands of their newborns became infected, and died in infancy.
- Elsewhere, "experts" had already given the BCG vaccine to 2,000,000 children and claimed it protected against TB.

1. We worried that docs might preferentially treat patients with better prognoses.

Two studies determined whether Public Health Physicians could reduce deaths of batches of NYC babies born into households with active TB by giving them BCG:

First batch: "Please give it to half of 'em."

Huge success: RRR for death <1 yr = 80%

1. Worried that docs might preferentially treat patients with better prognoses.

Second batch: 'Flipped a coin' to see which babies were to be given BCG (thus a 'fair comparison').

Huge failure: RRR for death <1 yr = 0%

Studied docs' decisions as to which babies to vaccinate in that first batch:

1. Worried that docs might preferentially treat patients with better prognoses.

Docs told to "give BCG to half of them" were preferentially treating babies:

- from wealthier families (less crowded, used more health services, etc).
- going to homes with less severe TB.

Less likely to die before the study began!

Am Rev Tuberculosis 1946;53:517-532.

1. There are modern-day replications of docs preferentially treating patients with better prognoses.

We were right to be worried.

1. Worried that docs might preferentially treat patients with better prognoses.

That's why RCTs employ:

- not only randomization
- but concealment (of allocations from treating clinicians)

The result → A fair(er) comparison of Rx

2. Worried that compliant patients might have better prognoses, regardless of Rx.

First confirmed in an RCT of treatments already in common use among heart attack survivors –

(based on positive clinical observations)

- that we hoped would reduce recurrent heart attacks and deaths.

2. Worried that compliant patients might have better prognoses regardless of Rx.

✓ Found that one of the drugs used on the basis of positive clinical observations (**estrogen**) actually increased deaths

✓ The RCT included one of the early, promising lipid-lowering drugs: **clofibrate**

Alas, Clofibrate didn't save lives.

- ✓ Participants randomized to Clofibrate had the same mortality as participants randomized to placebos.
- ✓ BUT, they found that one-third of the trial participants were non-compliant with their trial medications!
- ✓ So they re-analyzed the data, taking compliance into account.

Compliance in the Coronary Drug Project Trial

		Mortality Rate
Compliance with Clofibrate	Low (<80%)	
	High (\geq 80%)	16%

Compliance in the Coronary Drug Project Trial

		Mortality Rate
Compliance with Clofibrate	Low (<80%)	25%
	High (\geq 80%)	15%

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Relative Risk Reduction for Death among Clofibrate compliers = 40%

Compliance in the Coronary Drug Project Trial

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Compliance with Clofibrate	Low (<80%)	25%
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Relative Risk Reduction for Death among Clofibrate compliers = 40%

Number Needed to become Compliant with **Clofibrate** to save one more life = 10 !

NEJM 1980;303:1038-41

Compliance in the Coronary Drug Project Trial

- But Paul Canner decided to also look at the outcomes of participants randomized to take Placebos

Compliance in the Coronary Drug Project Trial

		Mortality Rate
Compliance with Placebo	Low (<80%)	28%
	High (\geq 80%)	

Compliance in the Coronary Drug Project Trial

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Compliance with Placebo	Low (<80%)	28%
	High (\geq 80%)	15%

Compliance in the Coronary Drug Project Trial

		Mortality Rate
Compliance with Placebo	Low (<80%)	28%
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Relative Risk Reduction for Death among
PLACEBO compliers = 46%

Compliance in the Coronary Drug Project Trial

		Mortality Rate
Compliance with Placebo	Low (<80%)	28%
	High (\geq 80%)	15%

Relative Risk Reduction for Death among
PLACEBO compliers = 46%

Number Needed to become
Compliant with the **PLACEBO**
to save one more life = 8 !

Could 'propensity scoring' have prevented the compliance bias?

1. Identified 40 baseline characteristics that might affect the risk of dying.
2. Statistically adjusted for all of them between participants who did and didn't take their placebos.

Could 'propensity scoring' have prevented the compliance bias?

3. "Propensity Corrected" Relative Risk Reduction in death from faithfully taking your placebo remained very high: 38%

($P < 0.000000007$!)

NEJM 1980;303:1038-41.

2. Worried that compliant patients might have better prognoses, regardless of Rx.

This 'placebo compliance' effect has been reported by several other investigators.

We were right to be worried.

Is a 'per-protocol' analysis (that excludes non-compliant participants) still an RCT?

2. Worried that compliant patients might have better prognoses, regardless of Rx.

That's why RCTs employ:

- intention-to-treat analyses of everybody who enters an RCT
- keeping track of everybody who enters an RCT

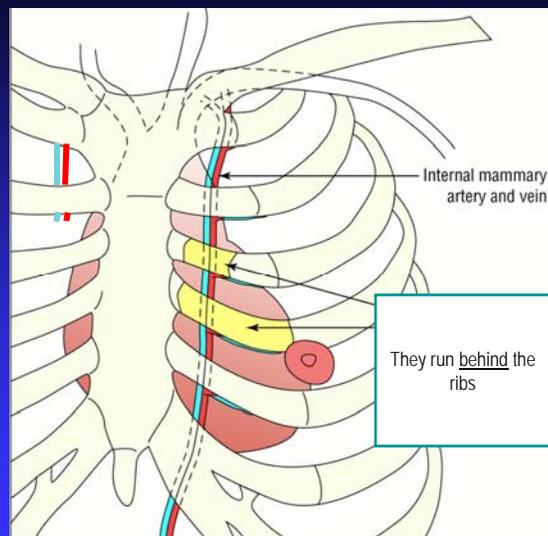
(My losses-to-follow-up among >12,000 trial participants in 16 countries = 0.4%)

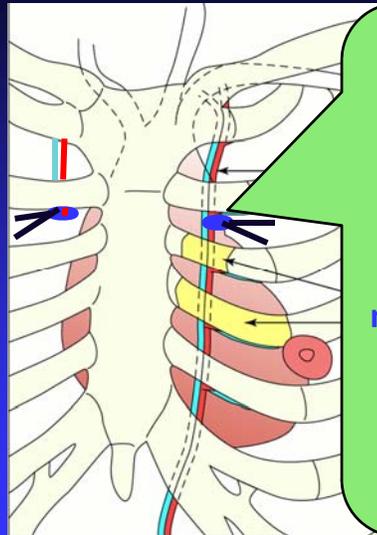
3. Worried that **patients** who liked their Rx might report spuriously better outcomes unrelated to its mechanism of action.

Ten years before we started doing RCTs, thousands of angina pectoris patients underwent a miracle operation.

Internal mammary artery ligation for angina pectoris

- ? a Genoan injected ink into cadavers' internal mammary arteries to see where it went . . .
. . . and found some of it in their coronaries!
- ✎ And suggested that tying off ('ligation') of internal mammary arteries ought to divert blood to the coronaries!





Simply tied off
("ligated")
the internal
mammary arteries
(on both sides)

Patients thought it worked wonders

complete or partial relief from the pain that accompanies the major types of heart disease has been obtained in nearly 80 percent of the several hundred operations performed to date.

A 1977 Retrospective on the landslide of these ligations

“It is, perhaps, surprising that between 1955 and 1960 there were still patients with angina whose mammary arteries were not ligated!”

Finally did an RCT of internal mammary ligation

1. Internal mammary arteries identified.
2. Loose ligatures placed around them.
3. Then randomized to:
 - tie them off!
 - or buzz off!

Conclusion from the RCT

“Bilateral skin incisions in the second intercostal space seem to be at least as effective as internal-mammary-artery ligation in the therapy of angina pectoris.”

Cobb LA et al. NEJM 1959;260:1115-8.

We were right to be worried.

3. Worried that **patients who liked their Rx** might report spuriously better outcomes unrelated to its mechanism of action

That's why RCTs employ:

- blinding patients when we can (including elaborate mock-procedures)
- “Hard” outcomes
- Blind adjudication of softer outcomes

The result → A fair(er) comparison of Rx

4. Worried that docs who liked their Rx might report spuriously better outcomes unrelated to its mechanism of action.

A Canadian RCT of promising drugs for MS (cyclophosphamide + plasma exchange) asked both 'blinded' and 'unblinded' neurologists to assess patient outcomes at 6, 12, and 24 months.

Neurologists liked the new Rx.

Results of the Canadian MS RCT:

'Blinded' docs reported no difference in MS outcomes between active and placebo Rx.

'Un-Blinded' docs reported better ($p < 0.05$) outcomes among patients on the active Rx at all 3 follow-ups.

We were right to be worried.

4. Worried that **docs** who liked their Rx might report spuriously better outcomes unrelated to its mechanism of action.

That's why RCTs employ:

Blinding the docs when we can.

“Hard” outcomes (e.g., all-cause mortality).

Blind adjudication of softer outcomes.

The result → A fair(er) comparison of Rx

So I reckon our worries are justified

1. Docs do preferentially treat patients with better prognoses.

2. Compliant patients do have better prognoses, regardless of their Rx.

3 & 4. Both Patients and Docs who like a Rx do report spuriously better outcomes unrelated to its mechanism of action.

That's why RCTs employ safeguards against the resultant unfair comparisons of Rx

- Randomization
- Concealed assignment of Rx
- Blinding of patients, docs, outcome assessors
- Intention-to-treat analyses
- Complete follow-up from the instant a participant enters a trial

And RCTs continue to evolve

Especially toward more 'generalizable' designs that are more widely applicable:

- Eg 1: In the HOPE Trial of CV-prevention, 46% are women, 86% are overweight, 38% have hypertension, and 28% are smokers.

And RCTs continue to evolve

Especially toward more 'generalizable' designs that are more widely applicable:

- Eg 2: Cluster trials like CHAP randomised entire communities to show how Pharmacy-based BP measurements integrated with a town's health care system lead to reduced hospital admissions for CVD.

And RCTs continue to evolve

Especially toward more 'generalizable' designs that are more widely applicable:

- Eg 3: "Firms Trials" that randomize patients to identical OPDs and wards with different therapeutic or organizational interventions
- (Care from established units + Outcomes from administrative data = lower costs per unit of useful new knowledge)

Can 'Comparative Effectiveness'
observational research solve these worries?

Well if their data sources tell them:

1. The patients docs selected to treat -

Can 'Comparative Effectiveness'
observational research solve these worries?

Well, if their data sources tell them:

1. The patients docs selected to treat -
2. Who knew the treatments they received-

Can 'Comparative Effectiveness' observational research solve these worries?

Well, if their data sources tell them:

1. The patients docs selected to treat -
2. Who knew the treatments they received-
3. and had to be compliant with filling their first and subsequent prescriptions-

Can 'Comparative Effectiveness' or other observational research solve these worries?

Well, if their data sources give them:

1. The patients docs selected to treat -
2. who knew the treatments they received-
3. and had to be compliant with filling their first and subsequent prescriptions-
4. and had which outcomes, as reported by them or their docs, neither of them blind.

They will have to be smarter than the
smartest clinicians (or anybody else!)
since Imhotep (circa 2600 b.c.)

Closing thought:

Bias is never 'cured' by adding more patients!

Is it time to retire the RCT ?

Conclusion from an international Symposium
of both trialists and non-trialists that
addressed this question in 2013:

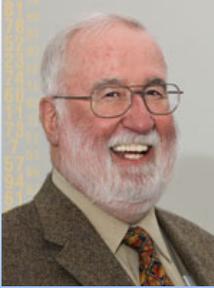
No



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