Pragmatic Trials: Why are they uncommon and difficult to implement?

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Disclaimer

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- The opinions I will express in this talk are not necessarily those of Richard Peto.

Have ***you*** ever done a pragmatic trial?

- Yesterday, the Cochrane Library listed 674,103 individual RCT reports.

- 829 were labelled pragmatic trials: 0.1%

This is not another "AIN'T IT A SHAME" talk

- Instead, it will ask:

1. Should pragmatic trials be more common?

2. Are there ways of making them less difficult to implement?

Quick Refresher: "Attitude" of Pragmatic Trials

Taken from Schwartz & Lellouch:

Pragmatic trials "enable us to compare two treatments under the conditions in which they would be applied in practice."

1. Treatments are "flexibly defined and usually complex"
2. "Takes account of auxiliary treatments"

“Attitude” of Pragmatic Trials

3. Includes “the possibility of withdrawals”

4. Criteria for effects “take into account the interests of the patients and the costs in the widest sense.”

5. Trial patients “predetermined as that to which the results of the trial are to be extrapolated.”

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- Yes, they do provide a fair comparison at the sites included in that pragmatic trial.

- But extrapolation ("generalizability") to other cites, cities, and countries is not automatic.

Should Pragmatic Trials be more common?

Everybody says so:

- Patient groups like the James Lind Alliance, etc.
- Planners/Payers like the Canadian Health Ministries
- Sponsors like the NIH Health Care Systems Research Collaboratory, etc.

Then, why are they uncommon?

- bigPharma stockholders see no profit in them
- Aren't very sexy for (young) trialists
- Haughty statisticians put them down as "imperfect experiments"
- Can be "difficult to implement"

Are there ways of making pragmatic trials less “difficult to implement”?

- Lots of well-thought-out (and sometimes pre-tested) strategies for overcoming legal, ethical, bureaucratic barriers have been presented elsewhere in this conference.

- Most are beyond the capacity (and patience!) of individual front-line pragmatic trialists to generate and implement (hence this talk).

(Assumes you've already suggested:)

- REBs ceding authority to single, fast Board (22 have done so far for Ontario Cancer Trials)

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- Phase 2 Futility Trials: Using hypothesized EER from your Phase 3 protocol, treat everybody to see whether your results are compatible.

  (could have prevented several dozen futile Phase 3 NINDB neuroprotective trials)

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Are there ways of making pragmatic trials less difficult to implement?

- While individual trialists are waiting, there are four things that they can do:

- N.B.: most will also aid explanatory trials

1. Greatly expand ‘Firms’ Trials

- 1880s: every 5th medical and every 4th surgical admission to Cook County Hospital went to the Homeopathy Service.

☠ (8% died there vs. 7% for the Allopathic Service).

- 1970s: Boston City admitted patients by strict rotation to the Harvard, Tufts, and Boston U. services.

 (Only compared outcomes once)

1. Greatly expand ‘Firms’ Trials

- 1980s: at Cleveland Metropolitan General Hospital, Brooke Army Medical Center Hospital, and University Hospitals of Cleveland:
- They took their multiple clinics and wards and combined (in-pt/out-pt) Services = Firms
- Randomly assigned:

➢ Clinical Staff

➢ Patients,

➢ & Interventions to different Firms.

‘Firms’ Trials have tested:

? Educational/behavioural strategies for more rational testing and treating (polypharmacy):

→ Worked (e.g., pneumovax increased x9)

? Special I-V line nurses:

→ Worked (Fewer complications)

? E/B strategies re: Routine hemoccult testing

→ Worked (Increased x12 {with no contamination across Firms}

Firms Trials Costs

1. ‘Selling’ the concept takes time and energy.
2. Once underway, assignments of staff and patients use resources and administrators already in place.
3. Outcomes typically determined from pre-existing routine administrative databases.
4. Costs often limited to the experimental intervention.

☺ One firms trial was over-funded by a bake/tee shirt sale

1. Greatly expand ‘Firms’ Trials

- Most Firms Trials are testing strategies for improving clinical competency and behaviour.
- But in-patient Firms are highly suitable for trials of short-term in-patient interventions.
- And Firms that extend into ambulatory care are well-suited for long-term pragmatic intervention trials.
- Neuhauser: Intl J Technol Ass in Health Care 1992;8:321-4.

2. Return to a single ethical standard

"We propose a remedy which would require the decision not to participate in an approved, available clinical trial to be subject to the same ethical requirements as trial entry."

(E. Segelov et al. Redressing the balance. Ann Oncol 1992;3:103-5)

If an REB-approved RCT is on at your institution

Then that RCT becomes the “standard of care” at your institution.

And if you are caring for a patient who is eligible:

It is unethical NOT to offer the trial to them

(If you don’t think your patient “can understand the trial treatment” and give informed consent to it . . .

. . . How on earth can they understand and consent to your treatment outside the trial?)

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c) Discontinue blind adjudication if early disagreement rates are trivial.

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d. Quit site visits for quality assurance and fraud detection

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- Replace them with central statistical monitoring (Janice Pogue et al, SCT this week)

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- Validate RADs against blinded individual clinical assessments in pre-trial pilot studies.
- If they pass, use ‘em.

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- RADs available for mortality.

Effects of #3 and #4 on Trial Costs

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CHAP **Pragmatic** Trial (Screening, referral, education, pharmacy support for elderly hypertensives) to reduce CVD hospital admissions plus death from any cause.	140,642 Over 65 y/o 13,379 Exp screened	$ 1.4 M In 2007	$ 1.5 M	$ 10 $ 110

And now for something entirely different

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Eg 1. Oz: deaths while waiting for ethics reviews.

Multicenter ethics review of a cancer trial in Oz

- Additional Australian lives saved per month from positive cancer trials = 30

- They concluded that 70 day Ethics Reviews cost 60 lives, and coined the term:

- DIABOLECAL (Delays in Accrual Brought On Largely by Ethics Committee Activity Lag-time).

[Int Med J 2007;37:680-6]

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- Surely we should insist that our ethics and regulatory colleagues answer this question.
- Let them quantify the "good"
- Let us quantify the harm:

Eg 1. Oz: deaths while waiting for ethics reviews.

Eg 2. Diversion of efforts from maintaining complete follow-up of randomized patients to filling out forms for REBs/regulators.

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☠ <5 additional events would trash 31% of them.

☠ For 1/3 of published RCTs, this number is <u>fewer</u> than the number of trial patients <u>lost to follow-up</u>.

Spring at the Trout Centre