

When Randomized Trials?

Adam La Caze

a.lacaze@uq.edu.au

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Aim

- 1 Argue the right question is *when*—as opposed to *whether*—randomized trials.
- 2 What conditions need to hold for a well-conducted randomized trial to be **confirmatory**.

Outline

- 1 Aim
- 2 Background**
 - The role of randomized trials
 - Why randomized trials?
- 3 Argument
 - Why randomized trials
 - When randomized trials
- 4 Conclusion

Randomized trials are confirmatory trials

- Well-conducted randomized trials play a “confirmatory” role in drug development (Sheiner, 1997).
- **Learning** trials focus on gaining a better understanding of the process or mechanism under investigation.
- **Confirming** trials focus on establishing that the expected outcomes of the process or mechanism eventuate.

Regulation → Therapeutic decisions

The hierarchy implies a clear course of action for physicians addressing patient problems: they should look for the highest available evidence from the hierarchy. (Guyatt and Rennie, 2002)

If a study wasn't randomized, we suggest that you stop reading it and go on to the next article in your search. (Straus et al., 2005)

Medicine → Social science

Most of us with rationalist pretensions presumably aspire to live in a society in which decisions about matters of substance with significant potential social or personal implications are taken on the basis of the best available evidence, rather than on the basis of irrelevant evidence or no evidence at all. Of course, the nature of what constitutes evidence in any particular instance could be a matter for significant debate. But, modulo such debate, most of us have the aspiration to live in a society which is more, rather than less, 'evidence based'.

Smith, 1996, p. 369

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Whether randomized trials?

- It is easy to find quotes that express *prima facie* support for the view that randomized trials are essential (or *sine qua non*) for medicine¹
- Urbach (1993) and Worrall (2002, 2007) argue against this view
- Randomization is practically necessary in particular domains—where “practically necessary” and the appropriate “domains” are often left unspecified.

¹Medical statisticians (Tukey, 1977); epidemiologists (Collins and MacMahon, 2007) and proponents of EBM (Sackett, 2006; Sackett et al., 1996)

Whether randomized trials?

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General arguments for randomized trials

- A positive role for randomizing can be given in a number of accounts of causation, including the manipulation and probabilistic accounts (Cartwright, 2010; Pearl, 2000; Steel, 2011; Woodward, 2003).
- In addition to frequentist arguments, good reasons can be given for Bayesians to randomize in certain contexts (including the testing of medical interventions) (Kadane and Seidenfeld, 1990; Lindley, 1982; Rubin, 1978; Suppes, 1982).

Cartwright (2011, 222)

Argument A:²

- A1 x plays a causal role in the principle that governs y 's production there.
 - A2 x plays a causal role here as well as there
 - A3 The support factors necessary for x to operate are present for some individuals here.
- Therefore, x plays a causal role here and the support factors necessary for it or operate are present for some individuals.

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For a trial to be **confirmatory**: (i) there needs to be a compelling argument for A1 and (ii) there exists an A for which a reasonable case can be made for A2 and A3.

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Why randomized interventional studies for testing the efficacy of interventions³

- 1 A high degree of unexplained variation in the response of subjects to the intervention
- 2 The benefits of new interventions are often small-to-modest and come with risks
- 3 Interventional studies have the capacity to rule out sources of error that alternative study designs do not, e.g. self-selection bias.
- 4 Randomization is the preferred method of allocation in interventional studies, and can be argued for on frequentist, Bayesian and pragmatic grounds.

³La Caze (2012)

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Designing a confirmatory trial

- Who will be recruited?
- What “dose” of the intervention will be given?
- How long will the intervention be given?
- What outcomes will be measured?

Conditions that enable confirmatory trials

- 1 Well understood and stable theoretical basis
- 2 Primary question is epistemic as opposed to ethical or political
- 3 Ability to meaningfully isolate the intervention of interest
- 4 Sufficient numbers of similar-enough participants/units of analysis

Rofecoxib harms

Example

- How long after a patient has ceased taking rofecoxib will they be at risk of adverse cardiovascular effects?
- Bresalier et al. (2005) demonstrated an increased risk of thrombotic events in patients receiving rofecoxib compared to placebo.
- But there was a discrepancy between the data reported in the trial and submitted to the FDA. (Lagakos, 2006; Nissen et al., 2006)
 - Trial included patients experiencing thrombotic events while taking rofecoxib or for 14 days following the last dose
 - Data submitted to the FDA data was analysed according to intention-to-treat (thrombotic events counted for all patients randomized rofecoxib).

Stability of the ethical and political basis of medical trials

- Some aspects of the theoretical basis surrounding medical interventions are remarkably stable.
 - The overall goal of research
 - What is considered a worthwhile benefit
- Randomized trials are more difficult to run and less likely to be confirmatory (or used) when contested ethical or political positions are central to the the design of the trial.

Example

Concrete examples arise in addiction research (Hall, 2008) and water policy (in South East Queensland at least) (Head, 2010).

Ability to meaningfully isolate the intervention of interest

- Many interventions in social science can't be isolated (e.g. class sizes discussed in Cartwright (2009))
- It is relatively easy within biology to identify, test and manipulate mechanisms—usually within purpose-built experimental models
- Social mechanisms are easy to propose, but difficult to establish and isolate

Units of analysis

- Need to be able to randomize a sufficient number of participants; e.g. randomizing schools or randomizing students.
- The participants need to be sufficiently similar in the relevant respects such that the effect of the intervention is constant (or can be assumed to be near-constant)
 - **Additivity**: the notion of the hope that there is some scale the statistician can find upon which the treatment effect makes a (near) constant difference (Senn, 2004, 3730)

Conclusion

- Context is important in the justification of randomized trials
- The contexts in which randomized trials play a confirmatory role is much more tied to the testing of new medicines than is typically appreciated
- Awareness of some of the conditions that enable confirmatory trials in testing medicines highlights the challenges facing the use of randomized trial in other contexts

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Outline

- 5 Appendix
 - Quotes on randomization

Randomization and therapeutic decisions

Many of us are convinced, by what seems to me to be very strong evidence, that the only source of reliable evidence about the usefulness of almost any sort of therapy or surgical intervention is that obtained from well-planned and carefully conducted randomized, and, where possible, double-blind clinical trials.

Tukey (1977, p. 679)