



Methods in health services research: Interpreting the evidence: choosing between randomised and non-randomised studies

Martin McKee, Annie Britton, Nick Black, Klim McPherson, Colin Sanderson and Chris Bain

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Methods in health services research

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Martin McKee, Annie Britton, Nick Black, Klim McPherson, Colin Sanderson, Chris Bain

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Correspondence to: Martin McKee
m.mckee@lshtm.ac.uk

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Evaluations of healthcare interventions can either randomise subjects to comparison groups, or not. In both designs there are potential threats to validity, which can be external (the extent to which they are generalisable to all potential recipients) or internal (whether differences in observed effects can be attributed to differences in the intervention). Randomisation should ensure that comparison groups of sufficient size differ only in their exposure to the intervention concerned. However, some investigators have argued that randomised controlled trials (RCTs) tend to exclude, consciously or otherwise, some types of patient to whom results will subsequently be applied. Furthermore, in unblinded trials the outcome of treatment may be influenced by practitioners' and patients' preferences for one or other intervention. Though non-randomised studies are less selective in terms of recruitment, they are subject to selection bias in allocation if treatment is related to initial prognosis.

These issues have led to extensive debate, although empirical evidence is limited. This paper is a brief summary of a more detailed review¹ of the impact of these potential threats.

Summary points

Treatment effects obtained from randomised and non-randomised studies may differ, but one method does not give a consistently greater effect than the other

Treatment effects measured in each type of study best approximate when the exclusion criteria are the same and where potential prognostic factors are well understood and controlled for in the non-randomised studies

Subjects excluded from randomised controlled trials tend to have a worse prognosis than those included, and this limits generalisability

Subjects participating in randomised controlled trials evaluating treatment of existing conditions tend to be less affluent, educated, and healthy than those who do not; the opposite is true for trials of preventive interventions

Threats to validity of evaluative research and possible solutions

Type of validity	Threatening factor	Proposed solution
Internal	Allocation bias (risk of confounding)	Randomisation
		Risk adjustment and subgroup analysis (analysis)
External	Patient preference	Preference arms or adjustment for preference (design)
	Exclusions (eligibility criteria)	Expand inclusion criteria
	Non-participation (centres/practitioners)	Multicentre, pragmatic design
	Not invited (practitioner preference or administrative oversight)	Encourage practitioners to invite all eligible patients
	Non-participation (patients)	Less rigorous consent procedures

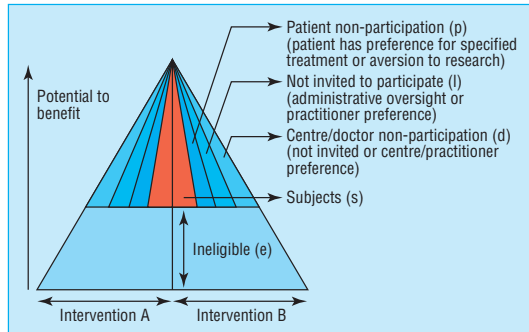


Fig 1 Differences in inclusion and participation. Shaded areas represent the study population

Nature of the evidence

The review focused on threats to internal and external validity of evaluations of effectiveness and on the strategies proposed to overcome them (table). Various factors act through their effect on the distribution of the potential to benefit among different groups. This can be illustrated schematically (fig 1). The reference population is defined by an envelope, represented here as a triangle but potentially taking many shapes. At some point, a threshold is reached, below which the overall risks outweigh the benefits. As patients are excluded or do not participate, the study population becomes a progressively smaller subset of the reference population, in principle increasing the scope for selection bias and raising the question of whether it is valid to apply the results obtained to the reference population.

We used systematic reviews to explore the potential and actual importance of factors that lead to selective recruitment, examining four questions:

- Do non-randomised studies give systematically different measurements of treatment effect from RCTs?
- Are there systematic differences between the subjects included in or excluded from studies, and do these influence the measured treatment effect?
- To what extent is it possible to overcome known or unknown baseline differences between groups that are not allocated randomly?
- How important are patients' preferences for an intervention and, if patients are randomised to a treatment they would not choose, how does this affect their outcome?

Findings

Comparing results of RCTs and non-randomised studies

Eighteen papers were identified where a single intervention was evaluated by both methods (a full list

is available on the *BMJ's* website). A review was published just after our original report; on the basis of eight comparisons it found that, on average, non-randomised studies overestimate effect size.² In contrast, of the seven studies in our review where the two methods detected effects in the same direction, in three the effect size was greater in the randomised trial and in four it was greater in the non-randomised study. The key finding in our study is that neither method consistently gave larger estimates of treatment effect.

In addition to chance, there are several potential explanations for different measurements of treatment effects. The overall impact will reflect the relative importance of each issue in a particular case. A randomised controlled trial may produce a greater effect if the patients enrolled in it receive higher quality care or are selected so that they have greater capacity to benefit than patients in non-randomised studies. But it may produce a lower estimate of treatment effect for several reasons:

- In non-randomised studies, patients tend to be allocated to treatments that are correctly considered most appropriate for their individual circumstances;
- Exclusions from a RCT create a sample with less capacity to benefit than in a non-randomised study;
- An unblinded RCT fails to capture patients with strong preferences for a particular treatment who show an enhanced response to treatment;
- Non-randomised studies of preventive interventions include disproportionate numbers of individuals who, by virtue of their health related behaviour, have greater capacity to benefit;
- Publication bias leads to negative results being less likely to be published from non-randomised studies than from RCTs.

The limited evidence indicates that the results of non-randomised studies best approximate to results of RCTs when both use the same exclusion criteria and when potential prognostic factors are well understood, measured, and appropriately controlled in non-randomised studies.³

In summary, the results of RCTs and non-randomised studies of similar patients may not, after adjustment, be substantially different in relative effect size. Any variations are often no greater than those between different RCTs or among non-randomised studies. Differences in effect sizes could be due to chance or differences in populations studied, timing, or nature of the intervention.

Exclusions

Randomised controlled trials vary widely in their inclusiveness. Medical reasons cited for exclusion from trials include a high risk of adverse effects and belief

London School of Hygiene and Tropical Medicine, London WC1E 7HT

Martin McKee
professor of European public health

Annie Britton
research fellow

Nick Black
professor of health services research

Klim McPherson
professor of public health epidemiology

Colin Sanderson
senior lecturer in health services research

University of Queensland Medical School, Brisbane 4006, Australia

Chris Bain
reader in social and preventive medicine

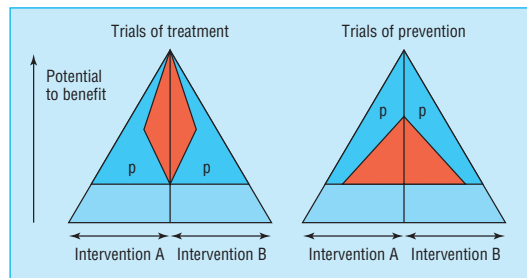


Fig 2 Effect of differences in participation in trials of prevention and of treatment. p=eligible non-participants; shaded areas represent the study population

that benefit, or lack of it, has already been established for some groups.

Scientific reasons include greater precision in estimating treatment effects by having a homogeneous sample,⁴ and reduced risk of bias by excluding individuals most likely to be lost to follow up.⁵ In addition, many RCTs have blanket exclusions,⁶ the reasons for which are often unstated, of categories of patients such as the elderly, women, and ethnic minorities.

Few studies have examined differences in prognostic factors between included and excluded patients, but some have used clinical databases to examine this.^{7,8} The patients included in such databases tended to have a poorer prognosis than those in trials: in one study, a subset selected to meet eligibility criteria of RCTs produced treatment effects of similar size to those obtained from RCTs.³

Participation

Evaluative research is undertaken predominantly in university or teaching centres, but non-randomised studies are more likely than RCTs to include non-teaching centres, and criteria for participation in RCTs may include the achievement of a specified level of clinical outcome. The available evidence suggests that this may exaggerate the measured treatment effect.⁹

Most evaluative studies fail to document adequately the characteristics of eligible patients who do not participate. The effect of non-participation differs between RCTs that evaluate interventions designed to treat an existing condition and those directed at preventing disease (fig 2).¹⁰ Participants in the former tend to be less affluent, less educated, and more severely ill than eligible patients who do not participate.¹¹ In contrast, participants in RCTs evaluating preventive interventions tend to be more affluent, better educated, and more likely to have adopted a healthy lifestyle than patients who decline.¹² On the basis of the evidence from the comparisons discussed earlier, it is plausible that low participation in RCTs of treatment may exaggerate treatment effects by including more skilful practitioners and subjects with a greater capacity to benefit, while RCTs of prevention may underestimate effects as participants have selectively less capacity to benefit.

Impact of patients' preferences

There is little empirical research on the impact on outcome of patients' preferences. The four studies that attempted to measure preference effects either were small or have yet to report full results.¹³⁻¹⁶ In theory, preference could have an important impact on results

of RCTs, especially where the true effect is small. Such effects could account for some observed differences between results of RCTs and non-randomised studies. There are methods that may detect preference effects reliably; though these may contribute to understanding this phenomenon, none provides a complete answer.¹⁷ This is mainly because randomisation between preferring a treatment and not is impossible, and confounding may bias any observed comparison.

Adjustment for baseline differences in non-randomised studies

Despite the evidence that the results of RCTs and non-randomised studies are often similar, differences in baseline prognostic factors clearly can be important. Absence of randomisation can produce groups that differ in important ways, and it is necessary to consider whether it is possible to adjust for such differences. Adjustment for imbalance in baseline prognostic factors between arms of non-randomised studies commonly changes the size of the measured treatment effect, but such changes are often small and inconsistent.¹

Overall, the limited evidence suggests that differences in the populations studied by RCTs and non-randomised studies are likely to be of at least as much importance in explaining any differences and that the two methods should be compared only after patients not meeting eligibility criteria for the RCT are excluded.

Recommendations

A large, inclusive, fully blinded RCT incorporating appropriate subgroup analysis is likely to provide the best possible evidence of effectiveness, but there will always be circumstances in which randomisation, especially on an inclusive basis, is unethical or impractical.¹⁸ In circumstances where there are genuine reasons for not randomising,¹⁹ non-randomised studies can provide useful evidence. In such studies, adjustment for baseline imbalances should always be attempted, as rigorously and extensively as possible, and the procedures should be reported explicitly to help readers' evaluations. However, adjustment cannot be relied on to approximate the prognostic balance of randomisation, given unknown or unmeasurable confounding.

Investigators conducting evaluative research (using any design) must improve the quality of reporting. Authors should define the population to whom they expect their results to be applied; what has been done to ensure that the study population is representative of this wider population, and any evidence of how it differs; whether centres that participated differ from those that declined; and the numbers and characteristics of patients eligible to be included who either were not invited to do so or were invited and declined.

The findings of such studies have implications for the way in which evidence is interpreted. When faced with data from any source, whether randomisation has been used or not, it is important first to pursue alternative (non-causal) explanations thoroughly and examine the possible influence of chance, bias, and confounding, perhaps using sensitivity analyses where feasible.

Where only non-randomised data are available, the potential for allocation bias should be considered and any attempts at risk adjustment should be assessed.

Where only randomised trials are found, preference effects should also be considered. To obtain an uncontaminated estimate of the physiological effect of a treatment, RCTs should be blind to everyone involved, but for many interventions this will be impossible. Also, the advantages of narrowing inclusion criteria to ensure high participation in RCTs should be balanced by the potential need for subgroup analysis. It should not be assumed that a summary result applies to all potential patients.

When both randomised and non-randomised studies have been conducted it is important to ascertain whether estimates of treatment effect are consistent for patients at similar risk across studies. If so, it may be reasonable to accept the results of the less exclusive non-randomised studies. Differences in results cannot be assumed to be solely due to the presence or lack of randomisation—differences in study populations, characteristics of the intervention, and the effects of patients' preferences may also affect the results.

Whichever design is used, generalisability needs attention. One approach involves examining the relation between reduction in relative risk (as a measure of effect size) against the percentage of events in the control arm (as an indirect measure of inclusiveness)²⁰; this is sometimes referred to as metaregression.²¹ Where sufficient data are available from RCTs, it may be possible to identify separate measures of benefit and harm. If, as has been shown for giving anti-coagulants to prevent stroke, the percentage reduction in relative risk remains constant at all levels of severity and the increase in absolute risk of an adverse effect remains constant, the reduction in absolute risk for a given patient can then be estimated.²²

In conclusion, RCTs and non-randomised studies can provide complementary evidence—but it is important that clinicians using this evidence are aware of the strengths and weaknesses of each method.

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