

EDITORIAL

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“...evidence suggests that well-conducted, randomized clinical trials remain one of the best ways to demonstrate the efficacy of an intervention or treatment.”

Trial effect: the road from efficacy to effectiveness

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There is a widespread belief that participation in a clinical trial provides an additional benefit called a ‘trial effect’. Yet there is limited empirical evidence that such a trial effect exists.

Trial effect: a sum of many effects

A trial effect is considered a benefit that trial participants experience merely by the act of trial participation. The experimental treatment effect, protocol effect, care effect, Hawthorne effect and the placebo effect, are all potential components of an overall trial effect and the terms ‘participation benefit’ or ‘participation effect’ have been used to cover four out of the five effects (excludes treatment effect). Similarly, older studies referred to a trial effect as an ‘inclusion benefit’ [1,2].

The experimental treatment effect is thought to occur when treatment offered in a study is better than the current standard of care and would be expected to accrue only to subjects randomized to the experimental therapy. The protocol effect is a possible benefit arising from closely adhering to the treatment regimens and procedures that are clearly outlined in the clinical trial’s manual. The care effect arises from differences in care between trial and non-trial participants that may not be specifically codified in the protocol. The Hawthorne effect is due to changes in patient or clinician behavior as a result of being under close observation in a trial. The placebo effect arises from psychologically mediated benefits associated with the administration of a sham or simulated intervention. The components of a participation effect are hypothesized to accrue to trial participants regardless of study arm and result in improved outcomes when comparing trial with non-trial participants.

Measuring a trial effect

Measurement of a trial effect, a composite of at least five known effects, is challenging as each effect could influence outcomes to varying degrees; the contribution of each effect to the overall trial effect may be different; and there is likely overlap between effects, such as placebo and care effect.

■ Comparison groups

The biggest challenge to trial-effect measurement is identifying the optimal control group. Ideally the control group should comprise non-trial participants that differ from trial participants only in trial participation. Theoretically, this group could be obtained by starting with an eligible study population and randomizing one group to trial participation and the other to non-trial participation. This would be ethically challenging and in practice is not achievable.

Keywords: care effect • effectiveness • efficacy • experimental treatment effect
• Hawthorne effect • placebo effect • protocol effect • trial effect

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Another option would be to prospectively identify all trial-eligible refusers. This group would have satisfied trial-entry criteria and were offered, but declined, participation in the trial. This option is both feasible and attractive, but is limited by the fact that intrinsic differences between trial-eligible refusers and trial participants may exist. Trial-eligible refusers might lack trust in the medical system, which may influence adherence to interventions and result in poorer outcomes. Additionally, if medical staff become aware of the data gathering on trial-eligible refusers, they may maintain records or provide care more carefully in this group, thereby introducing a component of a trial effect (Hawthorne effect or care effect) to non-trial participants.

A third option would be to prospectively compare trial participants with a group of eligible subjects who satisfied trial entry criteria but were not offered trial participation. Option four would be a retrospective comparison of trial participants with a group of eligible patients from the same population but who did not participate.

For options two, three and four, the most robust comparison can be made when: data gathered on the groups are congruent (type and timing of evaluations); both groups are drawn from a single study population to minimize baseline differences; and the treatment/intervention between the two groups are the same or similar. Statistical methods should be used to adjust for baseline imbalances and confounding. For the prospective study designs, every effort should be taken to avoid approximating trial procedures among the non-trial groups.

■ Bias & confounding

There are other important considerations when measuring a trial effect. Bias and confounding may either hide a true trial effect or create an apparent trial effect where none exists. Entry-eligibility criteria dictate trial-participant selection and may result in a healthier group of subjects with fewer comorbidities and thus more positive outcomes. More subtle bias not captured by eligibility criteria may also exist. Gender and race are associated with socioeconomic status, which can influence health-related behavior and the course of disease. Therefore, in order to truly attribute a trial effect to trial participation alone, the racial/ethnic, gender and age distribution of trial and non-trial participants must be comparable. Alternatively, if non-trial participants change their behaviors in ways that influence their treatment outcome, this may hide a true trial effect.

■ Additional considerations

Bias may arise due to a more careful, thorough and accurate measurement of outcome among the trial

participants relative to the non-trial participants. Data gathering within studies can be more complete and this may also be the case for maintenance of medical records.

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Measurement of a trial effect in a chronic illness might be different than for a more rapidly terminal illness, such as certain cancers. Frequently, patients with more advanced cancer diagnoses have limited options and might consider any intervention in the hope of extending life. Thus, patients who are more sick may opt for cancer trials, resulting in poorer outcomes. By contrast, in chronic diseases such as HIV or Type II diabetes, there is less urgency for newer, more experimental interventions, likely resulting in fewer differences between trial and non-trial participants. Surrogate markers (HIV RNA in HIV infection, HgbA1C in diabetes) used to measure outcomes should be objective, validated, accurate and readily and easily available outside a trial setting. Chronological time may also influence trial-effect measurement, with studies conducted at the inception of a new procedure/treatment showing a positive trial effect and no effect in more recent studies, due to widespread training, dissemination and acceptance of the new intervention [3].

Implications of a trial effect

A trial effect may be present or absent and if present may be positive or negative. A negative trial effect may arise from any of the following: strict adherence to protocol likely to limit access to complementary and alternative medicines/interventions beneficial to certain groups of patients; distrust of the medical community and of research may make the consent process for some racial and ethnic groups traumatic; continued interaction with the medical community, a requirement of trial participation, may place a negative psychological burden on these groups; the new intervention may just not be as good as the older intervention/standard of care. A true negative-trial effect may be missed due to very active trial monitoring by data and safety monitoring boards, institutional review boards and investigators with close adherence to ethical principles outlined by the Declaration of Helsinki and the Nuremberg code, resulting in early study modification or termination so that negative effects are not experienced by trial participants [4,101].

Presence of a positive trial effect raises the question of efficacy versus effectiveness. Clinical trial data are

used to establish care and treatment guidelines; by clinicians in clinical practice to provide evidence-based care; by pharmaceutical companies to support the superiority of a treatment/intervention; and to directly influence patients and providers behavior. If a true benefit to trial participation exists due to a trial effect that is beyond just the effect of the experimental treatment, then modification to clinical care that incorporates aspects of 'trial effect' may be needed to reduce disparity in response between trial and non-trial participants. Care effect likely arises in part from frequent, closely spaced in time study visits regardless of need and incorporation of this visit schedule into clinical care could result in better provider-patient relationships and improved patient education, leading to improved medication adherence and the improved outcomes associated with clinical trials. Currently, clinical care is highly individualized, whereas clinical trials are strictly protocol driven. Treatment regimens are carefully outlined in the trial protocol and consideration is also given to if, when and how deviations from protocol should be permitted. Protocol effect is another aspect of trial effect that might be included in clinical care.

In addition, finding no trial effect would suggest clinical equipoise between trial and non-trial participants for the same treatment/intervention and would address the widespread belief that participation in clinical trials confers added benefit not received in routine care. Second, it would help address a major concern regarding the external validity of clinical trials data. Clinicians would be reassured that extrapolating treatments from clinical trials to clinical practice does

not result in variations to treatment effects. Third, it reinforces the utility and applicability of treatment guidelines, which are generally formulated using data from clinical trials. Fourth, it would encourage patients to enroll in clinical trials by suggesting that there is no reduction in treatment effects in a trial compared with clinical practice. Knowledge of the absence of a trial effect would also enable investigators to enroll patients in clinical trials without over promising the benefits of trial participation.

Conclusion

Rigorous measurement of a trial effect, a composite of at least five known effects, is challenging. Establishing causality between trial participation as the unequivocal reason for improved outcomes remains elusive. Reassuringly, most evidence points to weak support favoring an added benefit to trial participation with no negative trial effect being reported [3,5–8,102]. Rather than detracting from the importance of clinical trials, this evidence suggests that well-conducted, randomized clinical trials remain one of the best ways to demonstrate the efficacy of an intervention or treatment.

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References

- Lantos JD. The 'inclusion benefit' in clinical trials. *J. Pediatr.* 134(2), 130–131 (1999).
- Silverman MA. Disclosing the 'inclusion benefit'. *J. Perinatol.* 22, 261–262 (2002).
- Menezes P, Miller WC, Wohl DA, Adimora AA, Leone PA, Eron JJ. Does HAART efficacy translate to effectiveness? Evidence for a trial effect. *PLoS ONE* 6(7), e21824 (2011).
- International Military Tribunal. Trials of war criminals before the Nuremberg Military Tribunals under Control Council law no. 10. Government Printing Office, Washington, DC, USA (1950).
- Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a 'trial effect'. *J. Clin. Epidemiol.* 54(3), 217–224 (2001).
- Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 363(9405), 263–270 (2004).
- Stiller CA. Centralised treatment, entry to trials and survival. *Br. J. Cancer* 70(2), 352–362 (1994).
- Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. *BMJ* 330(7501), 1175 (2005).
- 59th WMA General Assembly. WMA Declaration of Helsinki – ethical principles for medical research involving human subjects. www.wma.net/en/30publications/10policies/b3 (Accessed 1 January 2012)
- ECRI Institute. Patients' reasons for participating in clinical trials and effect of trial participation on patient outcomes. www.ecri.org/Documents/Clinical_Trials_Patient_Guide_Evidence_Report.pdf (Accessed 27 June 2008)