Similar care

From: Key Concepts for assessing claims about treatment effects and making well-informed treatment choices (Version 2022)

2.1b Consider whether the people being compared were cared for similarly.

Explanation

If people in one treatment comparison group receive additional treatments or more care and attention ("co-intervention") than people in the other comparison group, differences in outcomes may reflect those differences rather than the effects of the treatments being compared. For example, in a randomized trial of cognitive behavioural therapy (CBT) for hypochondriasis (persistent fear or belief that one has a serious, undiagnosed illness) compared with no cognitive therapy, a detailed letter of advice was sent to the primary care physicians whose patients were allocated to receive CBT *[Barsky 2004 (RS), Thomson 2007 (SR)]*. Thus, it was not possible to attribute any differences in outcomes to CBT alone since the letter could have altered how the primary care physicians managed patients allocated to CBT. In addition, patients in the CBT group received more attention than those who did not receive CBT. So, it is uncertain how much of the observed difference in outcomes was due to non-specific attention, support, concern, and positive expectation and not specifically to CBT.

Treatment providers who are aware of the treatment to which people are allocated may treat people differently based on their beliefs about the effectiveness of the treatments that are being compared. Their inclinations for or against the treatment can be transferred to the people receiving care and this could have an impact the outcome of interest. One way of preventing co-intervention is to keep treatment providers and patients unaware of ("blind" to) which people have been allocated to which treatment. However, this is not always possible. For example, a randomized comparison of acupuncture to relieve symptoms of irritable bowel syndrome compared three groups prior to administering genuine acupuncture to two of the groups *[Kaptchuk 2008 (RS)]*. Two groups received sham acupuncture. This blinded the recipients of care, but not the providers. To assess the impact of the providers' attitudes about the treatment, in one group, the providers were instructed to interact minimally with the patients, explaining that it was "a scientific study" for which they had been "instructed not to converse with patients". In the other group, they communicated with the patients in a warm, friendly manner, actively listened, showed empathy, and communicated confidence and positive expectation. The third group was put on a waiting list. The proportion of patients reporting adequate relief was 28% in the waiting list group, 44% in the sham acupuncture + minimal interaction group, and 62% in the sham acupuncture + positive communication group.

Basis for this concept

People who can potentially be "blinded" include the people receiving the treatments being compared, the people delivering the treatments, data collectors, people who assess the outcomes, data analysts, the data safety and monitoring committee, and manuscript writers. Because "double blinding" has multiple definitions and is interpreted in different ways *[Devereaux 2001 (RS), Schulz 2002]*, it is best to consider specifically who was blinded and how that could lead to overestimation or underestimation of treatment effects. A systematic review that compared effects in blinded and non-blinded studies in 142 meta-analyses *[Moustgaard 2020 (SR)]* categorised the comparisons and the potential for "performance bias" (the risk of co-intervention and placebo effects) and

measurement bias, based on who was not blinded and the type of outcome. The five categories and corresponding potential biases were:

	Who was not blinded	Types of outcome	Potential biases
1	Recipients of care	Patient reported	Measurement and performance
2	Recipients of care	Assessed by blinded observers	Performance
3	Providers of care	Assessed by providers	Measurement and performance
4	Providers	Assessed by blinded patients or observers	Performance
5	Outcome assessors	Outcomes requiring judgement ("subjective")	Measurement

The review found similar average effects for the two comparisons where there was a risk of performance bias and not measurement bias (comparison 2 and 4). This could reflect limitations of these comparisons, including possible confounding by other characteristics of the trials included in each meta-analysis, a small number of meta-analyses included in each comparison (14 and 13 respectively) and wide confidence intervals. It also is likely that a lack of blinding is sometimes associated with similar estimates, sometimes with overestimates of effects, and sometimes with underestimates of effects.

Another systematic review combined the data from seven studies that investigated the influence of blinding and other characteristics of randomized trials on treatment effect estimates *[Savović 2012b (SR)]*. It included 234 meta-analyses containing 1973 randomized trials. It found that, on average, lack of or unclear "double-blinding" (compared to double-blinding) was associated with average treatment effects that were 13% larger – despite differences in definitions of double-blinding. Exaggerated estimates of treatment effects were found primarily for subjective outcomes and not for objective outcomes. The extent to which that was due to measurement bias rather than performance bias is uncertain. Two other reviews have also found that, on average, treatment effects appeared to be exaggerated in randomized studies with lack of unclear implementation of double-blinding *[Martin 2021 (SR), Page 2016a (SR)]*, while other reviews have had inconclusive results *[Dechartres 2016 (SR), Wang 2021 (SR)]*. One other systematic review found that for subjective outcomes, effect estimates appeared to be exaggerated in trials with lack of or unclear blinding of participants (versus blinding of participants), but not for mortality *[Page 2016a (SR)]*. In contrast to that review, a systematic review of the association between lack of blinding and mortality results in critical care found slightly larger effect estimates in nonblinded trials *[Martin 2021 (SR)]*. A possible explanation for this finding is that physicians' beliefs in a favourable effect of new treatments might influence the timing of their decisions about end-of-life versus life-support practices. All these reviews included comparisons between studies and have a high risk of confounding by other characteristics of the trials included in each meta-analysis.

Within-trial comparisons are at low risk of confounding, when participants are randomized to be blinded or not to be blinded. A systematic review of randomized trials that included sub-studies that randomly allocated patients to be blinded or not blinded included 12 trials in its main analysis *[Hróbjartsson 2014a (SR)]*. It found that, on average, not blinding patients led to moderately exaggerated effect estimates in randomized trials of complementary and alternative treatments with patient-reported outcomes. It is uncertain to what extent this was due to measurement bias rather than performance bias. There are, however, other studies, like the acupuncture example in the explanation above, that indicate that attention from care providers and their attitudes can

sometimes influence outcomes (e.g., *[Guyatt 1984 (RS), Kaptchuk 2008 (RS), Thomas 1987 (RS)]*). So, if care providers are not blinded, their attitudes for or against a treatment can impact the outcome of interest.

It is not always possible to blind providers and recipients of care in randomized trials, and it is rarely possible in non-randomized studies such as cohort studies or case-control studies. However, it is possible to blind participants in, for example, comparisons of surgical and technical treatments, treatments that involve attention, devices, and physical therapy *[Armijo-Olivo 2017 (SR), Monaghan 2021 , Wartolowska 2014 (SR)]*, as well as in drug trials. When blinding is not possible, it is important to consider the possibility that there were differences in the treatments received in the treatment comparison groups besides the treatments being compared.

Implications

Be cautious about relying on the results of treatment comparisons if people in the groups that are being compared were not cared for similarly (apart from the treatments being compared). The results of such comparisons can be misleading.

References

Systematic reviews

Armijo-Olivo S, Fuentes J, da Costa BR, Saltaji H, Ha C, Cummings GG. Blinding in Physical Therapy Trials and Its Association with Treatment Effects: A Meta-epidemiological Study. Am J Phys Med Rehabil. 2017;96(1):34-44. https://doi.org/10.1097/phm.0000000000000521

Dechartres A, Trinquart L, Faber T, Ravaud P. Empirical evaluation of which trial characteristics are associated with treatment effect estimates. J Clin Epidemiol. 2016;77:24-37. https://doi.org/10.1016/j.jclinepi.2016.04.005

Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. Int J Epidemiol. 2014a;43(4):1272-83. https://doi.org/10.1093/ije/dyu115

Martin GL, Trioux T, Gaudry S, Tubach F, Hajage D, Dechartres A. Association Between Lack of Blinding and Mortality Results in Critical Care Randomized Controlled Trials: A Meta-Epidemiological Study. Crit Care Med. 2021;49(10):1800-11. https://doi.org/10.1097/ccm.0000000000005065

Moustgaard H, Clayton GL, Jones HE, Boutron I, Jørgensen L, Laursen DRT, et al. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. BMJ. 2020;368:l6802. https://doi.org/10.1136/bmj.l6802

Page MJ, Higgins JP, Clayton G, Sterne JA, Hróbjartsson A, Savović J. Empirical evidence of study design biases in randomized trials: systematic review of meta-epidemiological studies. PLoS One. 2016a;11(7):e0159267. https://doi.org/10.1371/journal.pone.0159267

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med. 2012b;157(6):429-38. https://doi.org/10.7326/0003-4819-157-6-201209180-00537

Thomson AB, Page LA. Psychotherapies for hypochondriasis. Cochrane Database Syst Rev. 2007;2007(4):Cd006520. https://doi.org/10.1002/14651858.cd006520.pub2

Wang Z, Alahdab F, Farah M, Seisa M, Firwana M, Rajjoub R, et al. Association of study design features and treatment effects in trials of chronic medical conditions: a meta-epidemiological study. BMJ Evid Based Med. 2021. https://doi.org/10.1136/bmjebm-2021-111667

Wartolowska K, Judge A, Hopewell S, Collins GS, Dean BJ, Rombach I, et al. Use of placebo controls in the evaluation of surgery: systematic review. BMJ. 2014;348:g3253. https://doi.org/10.1136/bmj.g3253

Research studies

Barsky AJ, Ahern DK. Cognitive behavior therapy for hypochondriasis: a randomized controlled trial. JAMA. 2004;291(12):1464-70. https://doi.org/10.1001/jama.291.12.1464

Devereaux PJ, Manns BJ, Ghali WA, Quan H, Lacchetti C, Montori VM, et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. JAMA. 2001;285(15):2000-3. https://doi.org/10.1001/jama.285.15.2000

Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman L, Jones NL, et al. Effect of encouragement on walking test performance. Thorax. 1984;39(11):818-22. https://doi.org/10.1136/thx.39.11.818

Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008;336(7651):999-1003. https://doi.org/10.1136/bmj.39524.439618.25

Thomas KB. General practice consultations: is there any point in being positive? BMJ. 1987;294(6581):1200-2. https://doi.org/10.1136/bmj.294.6581.1200

Other references

Monaghan TF, Agudelo CW, Rahman SN, Wein AJ, Lazar JM, Everaert K, et al. Blinding in Clinical Trials: Seeing the Big Picture. Medicina (Kaunas). 2021;57(7). https://doi.org/10.3390/medicina57070647

Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. Ann Intern Med. 2002;136(3):254-9. https://doi.org/10.7326/0003-4819-136-3-200202050-00022