The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

EDITORIAL

Check for updates

RESEARCH METHODOLOGY FOR THE OPHTHALMOLOGIST

Interpreting results from randomized controlled trials: What measures to focus on in clinical practice

Eye (2023) 37:3055–3058; https://doi.org/10.1038/s41433-023-02454-7

BACKGROUND

Randomized clinical trials are the gold standard for informing the effectiveness of therapeutic interventions, and often report a variety of effect measures that readers should consider [1]. Commonly used measures for dichotomous outcomes in randomized controlled trials include absolute risk, risk difference, relative risk, relative risk reduction, and odds ratio [1, 2]. These measures can be broadly categorized as conveying either absolute or relative effects and, depending on the choice of measure(s) used by authors, treatment effects may appear larger or smaller despite being based on the same data [1, 2]. This may lead clinicians to make different treatment decisions depending on how the results are presented [2–4]. Thus, it is imperative that clinicians understand how to interpret trial data, independently of the narrative of the sponsoring group, and be able to convey this information to patients to optimize shared decision-making.

Throughout this editorial we demonstrate how to identify, calculate and interpret different outcome measures for a two-arm, parallel-group, superiority randomised controlled trial described in Table 1 ref. [5]. We acknowledge that other trial designs such as non-inferiority trials may require alternative approaches to interpreting results. We describe and compare the measures of effect of laser trabeculoplasty compared to 0.5% timolol eye drops for glaucoma [5]. The dichotomous outcome, treatment failure, was assessed at 12 months post-randomization and defined as an intraocular pressure (IOP) greater than the target pressure depending on glaucoma severity [5]. We used a 2×2 table (Table 2) to capture information on treatment failure to aid in the visualization of study findings and the calculation of the different measures of effect using the equations presented in Box 1. Findings from the trial are presented in Table 3.

MEASURE OF ABSOLUTE EFFECT

Absolute risk

The absolute risk is defined as the probability that an event will occur [1, 2, 6]. We commonly refer to the risk of the adverse outcome in the control group as the baseline risk. Based on our example trial, the risk of treatment failure among participants who received timolol eye drops was 69% (121/176 = 0.69) compared to 39% (64/163 = 0.39) in participants who underwent laser trabeculoplasty. In other words, clinicians can expect that 69 individuals out of every 100 using timolol eye drops will experience treatment failure compared to 39 individuals out of every 100 who undergo laser trabeculoplasty.

Risk difference

The risk difference (RD), also known as the absolute risk reduction (ARR) [1, 2], allows trialists to describe the difference in outcome

Table 1. Study characteristics[a].

Author, year (*N* total)	Age (Mean, SD)	Female	Family history of glaucoma	SLT arm: number of participants and description of method	Timolol arm: number of participants and description of method	Stage of glaucoma	Previous Timolol eye drops
Phillipin, 2021 [5] $N_{Total} = 201$	66.3 (11.6)	41.3%	24% (same across arms)	$N = 101$ (191 eyes) Approximately 100 laser spots were applied to cover 360° of the trabecular meshwork. Starting energy level was 0·6 mJ, which was continuously titrated in steps of 0·1 mJ until cavitation bubbles appeared in around a third of laser spot applications.	$N = 100$ (191 eyes) 0·5% timolol eye drops administered twice daily	• Moderate: 48% • Advanced: 52% Note: similar % across arms	• SLT: 51 % • Timolol: 57%

[a]adapted from Phillipin et al. 2021 ref. [5].

Received: 22 December 2022 Revised: 10 January 2023 Accepted: 13 February 2023
Published online: 28 February 2023

Table 2. A 2 × 2 table.

Intervention	Outcome	
	Yes	No
Yes	a	b
No	c	d

Box 1. Measures of effect, and equations, for dichotomous outcomes

Measure of effect	Equation	SLT vs Timolol	Value
Absolute risk with intervention	a/(a + b)	SLT: 64/(64 + 99)	0.39
Absolute risk without intervention	c/(c + d)	Timolol: 121/(121 + 55)	0.69
Odds with intervention	a/b	SLT: 64/99	0.65
Odds without intervention	c/d	Timolol: 121/55	2.2
Relative difference	[c/(c + d)] - [a/(a + b)]	0.69-0.39	0.3
Relative risk	[a/(a + b)] ÷ [c/(c + d)]	0.39/0.69	0.57
Relative risk reduction	1 - Relative risk	1-	
Odds ratio	(a/b) ÷ (c/d) = ad/bc	0.65/2.2	0.30

rates using absolute terms (i.e., absolute risk in control group (timolol) – absolute risk in treatment group (laser)). Accordingly, the RD in our working example is 0.69-0.39 = 0.3. This can be interpreted as a 30% ARR in treatment failure with laser trabeculoplasty compared to timolol.

MEASURES OF RELATIVE EFFECT

Relative risk and relative risk reduction

In comparison to the measure of absolute effect, measures of relative effect are expressed as a ratio where the expected outcome in one group is assessed relative to that in the other [1, 2, 7]. The relative risk, also known as the risk ratio (RR), is the ratio of the risk or probability of an event in the intervention group (laser) to the risk of an event in the control group (timolol). As per the equation provided in Box 1 and the calculated risks per group, the RR in this case would be 0.39/0.69 = 0.57 or 57%. This may be interpreted as the risk of treatment failure with laser trabeculoplasty is a little more than half compared to patients treated with timolol eye drops. Another way to present this information is by using the relative risk reduction (RRR), which presents an estimation of how much less the risk is in the intervention group compared to the control group and is calculated as 1-RR. In our example, the RRR = 1-0.57 = 0.43 or 43% meaning that laser trabeculoplasty decreases the risk of treatment failure by a little less than half compared to timolol eye drops.

Odds ratio

Instead of assessing the risk of an event, we could look at the odds of an event occurring with or without the intervention by calculating the odds ratio (OR). The OR is the comparison (or ratio) of the odds of an event in the intervention group (laser) with the odds of that event in a control or reference group (timolol eye drops) [1, 2, 8, 9]. Going back to our example, the odds of treatment failure with laser trabeculoplasty is 64 (treatment failure) divided by 99 (treatment success) or 64/99 = 0.65, and the odds of treatment failure in the timolol eye drop group are 121/55 = 2.2. This yields an OR for the comparison of laser versus eye drops of 0.65/2.2 = 0.3. An OR < 1 indicates that there is a decrease in the odds of treatment failure occurring in those undergoing laser therapy, which indicates benefit of the intervention.

Table 3. Results in a 2 × 2 table from a randomized trial of selective laser trabeculoplasty compared with timolol eye drops for controlling intraocular pressure in adults with open angle glaucoma living in Tanzania[a].

Intervention	Outcome		Total
	Failure	Success	
Selective laser trabeculoplasty (SLT)	64	99	163
Timolol eye drops	121	55	176

[a]Data from Philippin et al. [5].

Clinicians generally find it is easier to interpret RRs that present event probabilities compared to ORs that describe the odds of events [1, 7, 9]. Fortunately, the OR and RR are interchangeable when the baseline risk is very low (i.e., the outcome is rare) [1, 7, 9]. Specifically, as the risk falls below 20%, odds and risk are more and more similar and nearly the same when the risk is under 10% ref. [9]. However, with higher risks substituting one for the other could be misleading and may over or under-estimate the treatment effect. In cases where the baseline risk is high, it is possible to calculate the risk from the odds using the following equation: risk = odds/ (odds + 1) ref. [10].

MEASURES TO FOCUS ON FOR CLINICAL PRACTICE

It is essential to differentiate between absolute (e.g., RD) and relative (e.g., RR or RRR) measures of effect, as relative measures may provide exaggerated effects or misleadingly large estimates especially when the baseline risk is low [1, 2, 6]. Let us assume two different risk groups, based on the severity level of glaucoma, a high-risk group with a hypothetical baseline risk of 20% for treatment failure and the low-risk group with a baseline risk of 2% (Fig. 1). In the high-risk group, a 50% RRR post intervention would decrease the absolute risk from 20% to 10%. A RD of 10% in terms of effect of the intervention is impressive. However, in the low-risk group with a baseline risk of 2%, a 50% RRR would decrease the risk from 2 to 1%, thus giving us a 1% RD, which is considerably less impressive and may not be worthwhile when considering other potentially relevant factors such as patient burden, costs, and potential harms.

Despite the importance of acquiring absolute measures of effect, doing so may require reading more than just the published abstract. We previously reviewed 96 Cochrane and 94 non-Cochrane systematic reviews of randomized trials and found that while 78% reported relative measures of effect for beneficial outcomes, only 23% reported absolute effects for these outcomes. The results for harms were worse; whereas 87% of reviews reported relative measures of effect for harms, only 13% reported absolute effect estimates for harms in their abstract. There was no difference in the proportion reporting absolute effects in the abstract between Cochrane and non-Cochrane reviews [11].

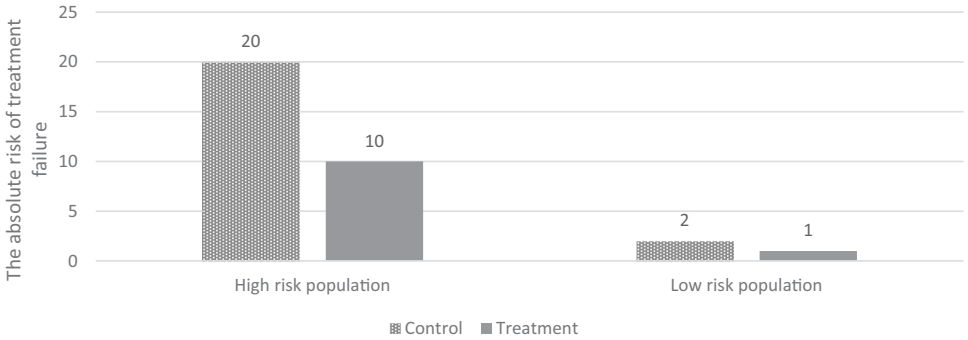

Fig. 1 Absolute Risk of Treatment Failure in Two Different Risk Groups Based on Severity Level. Example of a 50% relative risk reduction across different baseline risks comparing control groups (crosshatch) vs treatment groups (solid).

Considering how findings may be interpreted when presented with different effect measures, clinicians should be cautious about relative measures of effect and search out absolute measures. Ideally, trials should present both the RR and the RD so that two pieces of information are provided: the effect of the intervention (RR) and the difference in absolute risk with and without treatment (RD). However, if a trial fails to do so, which is often the case, clinicians can derive the RD by applying relative measures of effect to the patient's estimated baseline risk to inform patient discussions and guide clinical decision-making.

Andrea J. Darzi[1,2,3], Jason W. Busse[1,2,3], Mark Phillips[1], Charles C. Wykoff[4], Robyn H. Guymer[5], Lehana Thabane[1,6], Mohit Bhandari[1,7], Varun Chaudhary[1,7]✉ and for the Retina Evidence and Trials INternational Alliance (R.E.T.I.N.A.) Study Group*

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada. [2]Michael G. DeGroote National Pain Center, McMaster University, Hamilton, ON, Canada. [3]Department of Anesthesia, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada. [4]Retina Consultants of Texas, Blanton Eye Institute, Houston Methodist Hospital, Houston, TX, USA. [5]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, Melbourne, VIC, Australia. [6]Biostatistics Unit, St. Joseph's Healthcare-Hamilton, Hamilton, ON, USA. [7]Department of Surgery, McMaster University, Hamilton, ON, Canada. ✉email: vchaudh@mcmaster.ca

REFERENCES

1. Higgins JP, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. Cochrane handbook for systematic reviews of interventions, 2019. 2nd edn. (Wiley Online Library, https://doi.org/10.1002/9781119536604.ch6) 143–76.
2. Alhazzani W, Walter SD, Jaeschke R, Cook DJ, Guyatt G. Does Treatment Lower Risk? Understanding the Results. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. 3rd ed. USA: McGraw-Hill Education; 2015.
3. Forrow L, Taylor WC, Arnold RM. Absolutely relative: how research results are summarized can affect treatment decisions. Am J Med. 1992;92:121–4.
4. Naylor CD, Chen E, Strauss B. Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? Ann Intern Med. 1992;117:916–21.
5. Philippin H, Matayan E, Knoll KM, Macha E, Mbishi S, Makupa A, et al. Selective laser trabeculoplasty versus 0· 5% timolol eye drops for the treatment of glaucoma in Tanzania: a randomised controlled trial. Lancet Glob Health. 2021;9:e1589–99.
6. Barratt A, Wyer PC, Hatala R, McGinn T, Dans AL, Keitz S, et al. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ. 2004;171:353–8.
7. Prasad K, Jaeschke R, Wyer P, Keitz S, Guyatt G. Tips for teachers of evidence-based medicine: understanding odds ratios and their relationship to risk ratios. J Gen Intern Med. 2008;23:635–40.
8. Norton EC, Dowd BE, Maciejewski ML. Odds ratios—current best practice and use. JAMA. 2018;320:84–85.
9. Rochwerg B, Elbarbary M, Jaeschke R, Walter SD, Guyatt G. Understanding the Results: More About Odds Ratios. In: Guyatt G, Rennie D, Meade MO & Cook DJ, editors. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. 3rd ed. USA: McGraw-Hill Education; 2015.
10. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from https://www.training.cochrane.org/handbook.
11. Agarwal A, Johnston BC, Vernooij RW, Carrasco-Labra A, Brignardello-Petersen R, Neumann I, et al. Authors seldom report the most patient-important outcomes and absolute effect measures in systematic review abstracts. J Clin Epidemiol. 2017;81:3–12.

AUTHOR CONTRIBUTIONS

AD: Conception, analysis, interpretation, drafting JB: analysis, interpretation, drafting MP: analysis, interpretation, revising CW: analysis, interpretation, revising, final approval RG: analysis, interpretation, revising, final approval LT: analysis, interpretation, revising, final approval MB: analysis, interpretation, revising, final approval VC: analysis, interpretation, revising, final approval

COMPETING INTERESTS

AD: Nothing to disclose. JB: Nothing to disclose. MP: Nothing to disclose. CW: Nothing to disclose. RG: Nothing to disclose LT: Nothing to disclose. MB: Research funds: Pendopharm, Bioventus, Acumed—unrelated to this study. VC: Advisory Board Member: Alcon, Roche, Bayer, Novartis; Grants: Bayer, Novartis—unrelated to this study.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Varun Chaudhary.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

3058

FOR THE RETINA EVIDENCE AND TRIALS INTERNATIONAL ALLIANCE (R.E.T.I.N.A.) STUDY GROUP

Varun Chaudhary[1,7]✉, Mohit Bhandari[1,7], Charles C. Wykoff[4], Sobha Sivaprasad, Lehana Thabane[1,6], Peter Kaiser, David Sarraf, Sophie J. Bakri, Sunir J. Garg, Rishi P. Singh, Frank G. Holz, Tien Y. Wong and Robyn H. Guymer[5]