HHS Public Access

Author manuscript

JAMA Ophthalmol. Author manuscript; available in PMC 2022 April 18.

Published in final edited form as:

JAMA Ophthalmol. 2020 July 01; 138(7): 801. doi:10.1001/jamaophthalmol.2020.1864.

Stratification Clarification for Methods for Randomized Clinical Trials-Reply

Douglas A. Jabs, MD, MBA

Center for Clinical Trials and Evidence Synthesis, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland (Jabs); Wilmer Eye Institute, Department of Ophthalmology, Johns Hopkins University of Medicine, Baltimore, Maryland (Jabs).

Subgroup analyses typically are performed in randomized clinical trials. Proper subgroup analyses are performed on subgroups based on baseline characteristics and may be specified a priori or a posteriori. They are performed to determine if the results of the trial are potentially confounded and the treatment effects vary by subgroup. Subgroup differences in outcomes may be quantitative in nature (in that the effect is in the same direction but different in magnitude) or qualitative in nature (in that the effect is in a different direction than the overall trial results). A major problem with a posteriori–defined subgroup analyses is multiple comparisons. If 20 subgroups are analyzed, one might be expected to be different with a P value less than .05 by chance alone, and most often the number of a posteriori–defined subgroup analyses performed is not specified. This problem can be minimized by limiting the number of subgroups to only a priori–specified subgroups, using corrections for multiple analyses, and including interaction P values. However, despite using these precautions, subgroup results that are qualitatively different from the primary results should be viewed with great caution. This is true especially when the primary results do not show a difference between groups, but even when the primary outcome shows a difference between groups. Biologic plausibility and confirming the results of subgroup analyses in subsequent trials and/or demonstrating a consistent subgroup effect over several trials give confidence that the result is real and not by chance alone.1,2 Unfortunately, subgroups with a qualitative difference from the primary outcome typically cannot be replicated. Yusuf et al2 analyzed trials of β-blockers in patients with suspected or established myocardial infarction and found 9 trials in which there were subgroup differences followed by attempted replication of the results in subsequent trials. None could be replicated, causing the authors to encourage skepticism toward most reported subgroup outcomes and conclude that "…the overall 'average' result of a randomized clinical trial is usually a more reliable estimate of treatment effect in the various subgroups examined than are observed effects in the individual subgroups."2(p97) The First-line Antimetabolites as Steroid-Sparing Treatment Trial analyzed a priori–specified subgroups based on anatomic class of uveitis and suggested that there was a qualitative difference in the relative response to the 2 drugs in the posterior uveitis and panuveitis subgroup.3 Although methotrexate was noninferior to

Corresponding Author: Douglas A. Jabs, MD, MBA, Johns Hopkins University Bloomberg School of Public Health, 615 N Wolfe St, Room E7138, Baltimore, MD 21205 (djabs@jhmi.edu).

Conflict of Interest Disclosure: None reported.

mycophenolate overall, it appeared superior in the posterior uveitis/panuveitis subgroup. The apparent superiority in this subgroup was balanced by a nonsignificant superiority of mycophenolate in the intermediate uveitis subgroup, an analysis limited by the sample size of the intermediate uveitis subgroup.3 As noted, the more likely estimate of the treatment effect in both these subgroups is not the qualitatively different subgroup analysis, but rather the putative average result of the trial overall.2,4 The authors' comment (in the conclusion of the abstract)3 that the hypothesis-generating subgroup analysis based on anatomic class warrants further research is the correct interpretation of these data.

References

1. Meinert CL. Clinical Trials: Design, Conduct, and Analysis. 2nd ed. Oxford University Press USA; 2012:288–292.
2. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials.JAMA. 1991;266(1):93–98. doi:10.1001/jama.1991.03470010097038 [PubMed: 2046134]
3. Rathinam SR, Gonzales JA, Thundikandy R, et al. ; FAST Research Group. Effect of corticosteroid-sparing treatment with mycophenolate mofetil vs methotrexate on inflammation in patients with uveitis: a randomized clinical trial.JAMA. 2019;322(10):936–945. doi:10.1001/jama.2019.12618 [PubMed: 31503307]
4. Jabs DA. Antimetabolite therapy for uveitis: methotrexate or mycophenolate? JAMA Ophthalmol. 2019;137(12):1449–1451. doi:10.1001/jamaophthalmol.2019.3964 [PubMed: 31503274]