Outcome adjudication in randomised trials in leading medical journals: Protocol for a methodological review

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Background

Adjudication of outcomes is common in randomised trials. The aim of this process is to reduce random error in outcome assessment, and if local outcomes assessors are not blind to treatment assignment, to additionally reduce systematic error. In the last decade, many studies have begun to investigate the benefit of outcome adjudication in many clinical areas, including cardiovascular research[1,2], cancer studies[3] and also across all general medical fields[4]. Recommendations have been provided that suggest that adjudication of outcomes is more important when local outcome assessors are not masked to treatment allocation, where the adjudication process can assist in controlling systematic error (or limit detection bias)[4, 5].

However, it is not clear whether adjudication is still prevalent in trials in which outcome assessors are appropriately masked to treatment allocation, and if so, what the rationale is for adjudicating outcomes in such studies. The aim of this methodological review is to assess recently published randomised trials in leading medical journals to evaluate: (1) the proportion of trials that adjudicate their primary outcome; (2) the characteristics of these trials, including the blinding status of the local outcome assessors; (3) the types of outcomes that are adjudicated; (4) the adjudication process that is implemented in these trials; and (5) the rationale for trials to include outcome adjudication in their studies.

Eligibility

To be eligible for this methodological review, articles must meet the eligibility criteria below:

- Describe the primary results of a randomised trial

- Published in 2022 in one of the five following medical journals (classified as "leading" medical journals for the purpose of this study): The Lancet, The New England Journal of Medicine, The Journal of the American Medical Association, The BMJ, Annals of Internal Medicine
- Adjudicated their primary outcome

Note to enable us to meet our first aim, we will also collect minimal information on studies that would have been eligible but that did not adjudicate their primary outcome (see Data extraction section for more information of what data will be collected on these studies).

Screening

Screening will involve two stages: title and abstract screening, followed by full text screening. Initially, both reviewers will screen the same random sample of 10% of titles and abstracts. Following acceptable agreement (percent agreement > 90%), both review authors will then independently screen the remaining 90% without duplication. A similar process will be used for full text screening, with a same random sample of 10% of potentially eligible full texts first double screened, and if agreement between reviewers is acceptable (percent agreement > 90%), the remainder will be screened without duplication. At both stages, if agreement on the initial 10% is lower than 90%, then both reviewers will screen a further 10% in duplicate until agreement meets this threshold or the screening is complete.

Data extraction

A standardised data extraction form will be piloted on five articles that would be otherwise eligible, except that they were published in a different year to 2022. Once refinements have been made, both reviewers will double extract data from 10% of the eligible articles. As with the screening process, if there is excellent agreement (percent agreement > 90%) then both review authors will independently extract data from the remaining eligible articles. The data that we will extract includes:

1. Administrative information (Date of extraction, name of extractor, title of publication, journal and contact details of corresponding author)
2. Characteristics of the trial (Medical field, trial design and setting, number of participants randomised, number of sites, type of intervention and comparator, blinding status of participants and local site assessors and funding source)
3. Information on the primary outcome (and any other outcomes adjudicated)
4. Details of the adjudication process for the primary outcome (Blinding status of adjudicators to treatment allocation and site-assessment, how cases were selected for adjudication, information provided to adjudicators, number of adjudicators in the trial and per case, method use to deal with disagreements between adjudicators, and independence of adjudicators)

Once finalised, a blank copy of the data extraction form will be uploaded alongside this protocol, providing the specific details on the exact data that will be extracted.

Note that we will also extract minimal information about any randomised trials that would otherwise be eligible but did not adjudicate their primary outcome, to meet the first of our five aims. This minimal information will include:

- Medical field
- Number of participants randomised
- Number of sites
- Blinding status of local outcome assessors
- Description and subjectivity of primary outcome

Extracting this information will enable us to meet the first of our five aims, that is what is the proportion of trials that adjudicate their primary outcome. Further, this will permit a comparison of these minimal characteristics to establish whether important differences exist between the trials that do and do not adjudicate their primary outcome.

We will also contact authors of eligible trials with a brief questionnaire to ascertain their rationale for adjudicating outcomes in their randomised trial (see aim #5). The corresponding author from each publication will be contacted by email, with a reminder email if no response is received within 2 weeks. The information we will ask includes:

- Why did you adjudicate your primary outcome? What was the rationale for this?
- Was this costed?
- What were your experiences? Would you do it again in future trials?

Determining objectivity of outcomes

We will follow the approach of Ndounga Diakou et al.[4] and Moustgaard et al.[6] in determining whether outcomes are subjective or objective. We consider an outcome as subjective if their assessment was based on some form of judgement from the assessor and thus could be affected by knowledge of treatment allocation.

Analysis

All analysis will be descriptive using Stata software (version 16.1 or later). Mann-Whitney U tests, χ^2 tests, and Fisher exact tests will be used to assess comparability between randomised trials that did and did not adjudicate their primary outcome (e.g., eligible studies and those that would have been eligible if they had adjudicated their primary outcome).

Competing interests

No competing interests exist

References

1.   Pogue J, Walter SD and Yusuf S. Evaluating the benefit of event adjudication of cardiovascular outcomes in large simple RCTs. *Clin Trials* 2009; 6: 239-251. 2009/06/17. DOI: 10.1177/1740774509105223.

2.   Godolphin P, Bath P, Algra A, et al. Outcome Assessment by Central Adjudicators Versus Site Investigators in Stroke Trials: A Systematic Review and Meta-Analysis. *Stroke* 2019; 50: 2187-2196. DOI: 10.1161/STROKEAHA.119.025019.

3.   Dello Russo C, Cappoli N and Navarra P. A comparison between the assessments of progression-free survival by local investigators versus blinded independent central reviews in phase III oncology trials. *European Journal of Clinical Pharmacology* 2020; 76: 1083-1092. DOI: 10.1007/s00228-020-02895-z.

4.   Ndounga Diakou LA, Trinquart L, Hróbjartsson A, et al. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. *Cochrane Database of Systematic Reviews* 2016. DOI: 10.1002/14651858.MR000043.pub2.

5.   Godolphin PJ, Bath PM and Montgomery AA. Should we adjudicate outcomes in stroke trials? A systematic review. *International Journal of Stroke* 2022: 17474930221094682. DOI: 10.1177/17474930221094682.

6.   Moustgaard H, Bello S, Miller FG, et al. Subjective and objective outcomes in randomized clinical trials: definitions differed in methods publications and were often absent from trial reports. *Journal of Clinical Epidemiology* 2014; 67: 1327-1334. DOI: https://doi.org/10.1016/j.jclinepi.2014.06.020.