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REVIEW ARTICLE

Inadequate planning and reporting of adjudication committees in clinical trials: Recommendation proposal

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Abstract

Objectives: Adjudication committees (ACs) are recommended in randomized controlled trials (RCTs) to standardize the assessment of events. We aimed to assess the reporting and functioning of ACs (synonyms: clinical event committees, endpoint committees) in clinical trials.

Study Design and Setting: We searched five high-impact-factor medical journals for reports of RCTs with clinical event endpoints published between January 1, 2004 and December 31, 2005.

Results: ACs were reported in 33.4% of the 314 reports of RCTs. ACs were reported in 29.6% of trials with low risk of misclassification (i.e., ''hard'' main outcome), in 47.5% of trials with medium risk of misclassification (i.e., subjective main outcome and intervention delivered in a blinded fashion) and in 31% of trials with high risk of misclassification (i.e., subjective main outcome without intervention delivered in a blinded fashion). Selected cases to be adjudicated consisted largely of events identified by site investigators (93.3%). Data provided to the AC were reported for 47.4% of ACs.

Conclusion: Reporting of ACs is not fitted to the risk of biased misclassification. Important aspects of the functioning of ACs are insufficiently reported or raise methodological issues. We propose some recommendations for planning and reporting ACs in clinical trials.

Keywords: Randomized controlled trials; Adjudication committee; Clinical event committee; Endpoint committee; Classification bias; Recommendations

1. Introduction

The main purpose of a randomized controlled trial is to obtain a valid estimate of the treatment effect. The process of outcome assessment has a direct impact on the study results [1]. Determining whether a patient has reached an event may be difficult if the decision involves some subjectivity or when the endpoints require the application of a complex definition. Moreover, when the intervention is not delivered in a blinded fashion, the risk of ascertainment bias is high [2]. For this reason, the Food and Drug Administration (FDA) [2] and the European Medicine Agency (EMEA) [3] recommend assessment of events by adjudication committees (ACs) in guidelines published in November 2001 and July 2005, respectively.

The EMEA defines an AC as a committee consisting of clinical experts in a specific clinical area whose aim is to harmonize and standardize endpoint assessment. Synonyms are ''clinical endpoint committee,'' ''clinical event committee,'' and ''panel review committee.'' The importance of such committees has been outlined in several studies [1,4−8] showing that the classification of events changed in about 20%−30% of cases after assessment by an AC. These modifications could have an important impact on treatment effect estimates, as demonstrated by Naslund et al. [6], who showed that a four-member AC, after examining case report forms transmitted by local investigators, corrected misinterpretations in 28.3% of cases leading to significantly different results from the preliminary results provided by site investigators.

There is no recommendation on how ACs should process to ascertain endpoints and little is known about what is reported in RCTs concerning the functioning of ACs (e.g., number of members in the AC, how cases to adjudicate are selected, and reviewing process). We systematically reviewed RCTs published in 2004 and 2005 in five

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high-impact-factor general medical journals to assess the reporting of ACs to ascertain clinical event endpoints and to describe the reported process of adjudication.

2. Material and methods

2.1. Data sources and searches

We performed a computerized search in MEDLINE (via PUBMED) to identify all reports of RCTs published in 2004 and 2005 in five high-impact-factor general medical journals (*New England Journal of Medicine*, *Lancet*, *JAMA*, *Annals of Internal Medicine*, *BMJ*) from January 1, 2004 to December 31, 2005 with ''randomized controlled trials'' as the limit. Our goal was not to be exhaustive but, rather, to raise awareness of methodological issues concerning ACs. We chose these five journals because (1) they publish a high number of RCTs in many medical areas; (2) they have a high impact factor which is a good predictor of high methodological quality of journal articles [9]; and (3) they are also considered as having a higher quality of reporting than the others [10,11].

2.2. Study selection

One of us (A.D.) selected potentially relevant articles after screening titles, abstract and material and methods sections. Articles were included if the study was a RCT having an event as a primary or secondary outcome. An event was defined as an outcome that may or may not occur for each subject in the RCT, anytime during the study period. Trials reported as phase 1, 2, or pilot studies or assessing the efficacy or safety of diagnostic or screening procedures were excluded, as were subgroup analyses, secondary analyses, and follow-up studies from an RCT. Articles were screened for duplicate publication (i.e., the same trial described in several articles), and only the trial with the main results (i.e., the article reporting the results for the primary outcomes) was selected. When articles referred to a former publication for methodology (e.g., publication of the protocol), this publication was searched and also evaluated.

2.3. Data extraction

We used a data collection form that had been developed after an extensive bibliography on the subject and previously tested by two reviewers (A.D. and I.B.) on a random sample of 10 reports published in 2003. One reviewer (A.D.) independently completed all the data extractions. A second member of the team (I.B.) reviewed a random sample of 30 articles to assess interrater agreement. In case of discrepancies between the abstract and the full text, the reviewers relied on the full text. The reviewers were not blinded to the journal name and authors.

Data were obtained from each article as specified below.

1. Characteristics of the selected articles, including medical area, funding sources (public, private, both public and private, or unclear), type of treatment assessed (pharmacological, nonpharmacological, or both), number of centers involved, and sample size. We also assessed whether patients, care providers, and outcome assessors were reported as blinded to the treatment arm.
2. Description of the primary and secondary outcomes: events were classified in several categories derived from previous studies [12–14]: death from all causes, death from a specific cause (e.g., cardiac death), therapeutic decisions (e.g., angioplasty, blood transfusion), and non-fatal medical events (1) involving a complex definition (e.g., myocardial infarction, stroke), (2) whose diagnostic relies only on radiological tests (e.g., stent stenosis, myocardial revascularization), and (3) whose diagnosis relies only on biological tests (e.g., diabetes). We also checked whether events were of the same medical area or needed the expertise of physicians from different fields, such as myocardial infarction and stroke.
3. Reporting and functioning of ACs: for each selected article, we looked for the reporting of an AC by searching all possible synonyms (e.g., adjudication committee, endpoint committee, clinical event committee, panel review committee) in the article as well as in the appendix and acknowledgment sections, the online extra material and the published protocol if possible. For each article reporting an AC, we noted
   - Methods for selecting cases to adjudicate: we reported whether the AC assessed the endpoints for all patients included in the RCT or only patients suspected of having an event according to site investigators or whether other methods for tracking events, such as national registries or development of a specific computer algorithm were used.
   - Type of information provided to the AC: we observed whether the information included the complete medical file for each patient, only some elements of the file or a standardized case report form; we also noted whether results of different tests were reported as being provided to the ACs.
   - Composition of the AC: we checked the size of the AC, the name of members, their field of skill and their training before adjudication began; we also noted whether the members of the AC were reported to be independent of the study or blinded to the treatment arm.
   - Reviewing process of the AC: we searched whether the outcomes to adjudicate were defined and reporting on the number of members reviewing each case and the process used to reach consensus. We checked for the reporting of a comparison between the results of the AC evaluation and the site investigators' evaluation.