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Systematic Reviews

The Reporting of Treatment Nonadherence and Its Associated Impact on Economic Evaluations Conducted Alongside Randomized Trials: A Systematic Review

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ABSTRACT

Objectives: To review trial-based economic evaluations, identifying 1) the proportion reporting adherence, 2) methods for assigning intervention costs according to adherence, 3) which participants were included in the economic analysis, and 4) statistical methods to estimate cost-effectiveness in those who adhered. We provide recommendations on handling nonadherence in economic evaluations. **Methods:** The National Health Service Economic Evaluation Database was searched for recently published trials. We extracted information on the methods used to assign shared costs in the presence of nonadherence and methods to account for nonadherence in the economic analysis. **Results:** Ninety-six eligible trials were identified. For one-off interventions, 86% reported the number of participants initiating treatment. For recurring interventions, 56% and 73%, respectively, reported the number initiating and completing treatment, whereas 66% reported treatment intensity. Most studies (23 of 31 [74%] trials and 42 of 53 [79%] trials of one-off and recurring interventions, respectively) reported strict intention-to-treat or complete case analyses. A minority (3 of 31 [10%] and 7 of 53 [13%], respectively), however, performed a per-protocol analysis. No studies used statistical methods to adjust for nonadherence directly in the economic evaluation. Only 13 studies described patient-level allocation of intervention costs; there was variation in how fixed costs were assigned according to adherence. **Conclusions:** Most of the trials reported a measure of adherence, but reporting was not comprehensive. A nontrivial proportion of studies report a primary per-protocol analysis that potentially produces biased results. Alongside primary intention-to-treat analysis, statistical methods for obtaining an unbiased estimate of cost-effectiveness in adherers should be considered.

Keywords: adherence, compliance, economic evaluation, systematic review, trial.

Introduction

Treatment adherence has been defined as the degree of correspondence between a participant's intended treatment and his or her actual treatment [1]. Those who are unable to adhere to their allocated treatment because they experience adverse effects, for example, are more likely to have poorer clinical outcomes and may also have higher health care costs [2,3]. Randomized controlled trials (RCTs) are often considered the criterion standard for assessing the cost-effectiveness of health care interventions. The prevalence of treatment nonadherence in RCTs, however, can be nontrivial [1]. Without clarity in reporting nonadherence and the methods used to accommodate it, the findings from a randomized trial may be difficult to interpret.

Recent reviews of RCTs have highlighted vague and incomplete reporting of adherence and inconsistency in how nonadherence was incorporated in the analysis [1,4]. Trial-based economic evaluations potentially suffer from similar shortfalls in reporting; however, this has not previously been investigated as part of a systematic review. The Consolidated Standards of Reporting Trials (CONSORT) statement supports "intention-to-treat" (ITT) analyses, which include all participants in the analysis group to which they were randomly allocated regardless of treatment adherence [5]. The major benefit of ITT analysis is that it preserves randomization and therefore eliminates selection bias in estimates of the treatment effect and cost-effectiveness. Because ITT analyses do not require adherence information, however, this may reduce the motivation for collecting and reporting adherence. Information on treatment adherence allows a more detailed exploration and understanding of the costs and effects of treatment. For example, adherence information can allow estimation of treatment cost-effectiveness in participants who adhere to the intervention,

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thereby informing policymakers in other settings in which adherence is different from that of the RCT [6].

There has been little discussion about the unique challenges presented by nonadherence in trial-based economic evaluations. For example, shared (or overhead) costs might be allocated equally across all those randomized to the treatment or, alternatively, allocated to individuals according to how much treatment they actually received. Furthermore, the type of nonadherence is potentially important for economic evaluation. A prescription collected from the pharmacy but not taken costs more than a prescription written but never filled. Because nonadherence is likely to be correlated with both costs and outcomes of care, the methods used to account for it might also affect the inference drawn from the cost-effectiveness summary measure. Therefore, it is important that trial-based economic evaluations are transparent about the extent of nonadherence and the methods used to account for it.

The aim of this article was to review published economic evaluations conducted alongside randomized trials and identify 1) the proportion reporting information on adherence to the randomized treatments, 2) the methods used for assigning intervention costs to participants according to adherence, 3) which randomized individuals were included in the primary economic analysis, and 4) statistical methods used to estimate intervention cost-effectiveness in those who did adhere to it. We also provide recommendations on improved handling of nonadherence in trial-based economic evaluations.

Methods

Search Strategy

The National Health Service Economic Evaluation Database (NHS EED) provides structured abstracts for most of the economic evaluations in the medical literature [7]. We searched the NHS EED for studies that contained a reference to randomization or an RCT by using the search terms "randomi*" and "RCT." We included economic evaluations with patient-level resource-use data collected between randomization and the primary assessment of outcome in an individually randomized parallel-arm RCT of a health care intervention. Exclusion criteria were non-RCTs, no economic evaluation detailed in the methods, cluster and crossover randomized trials and other designs with within-patient comparisons, trials in which the observational unit for adherence was not the participant, feasibility studies, models or long-term follow-up studies (even if partially based on RCT data), and studies not published in English.

We conducted our search in February 2013 and restricted it to studies published in 2011. This provided a sufficient number of articles reflecting recent methodological practice, and NHS EED abstracts were not complete for all studies published more recently.

For economic evaluations that referred to a main trial article (potentially with more information on treatment adherence), we reviewed both together.

All data were extracted by one author (S.L.B.) using a prespecified proforma. For studies in which there were uncertainties about classification, a second author (W.H.) also reviewed the article, and consensus was reached through discussion.

Experimental Treatment Arm

For each trial, we designated an experimental treatment arm for our analysis. Typically, this was the most experimental, newest, or highest intensity (e.g., dose) treatment. In situations in which this could not be determined (16 trials, 17%), we arbitrarily chose the first treatment arm mentioned within the Methods section of the economic evaluation article.

Nonadherence and Treatment Intensity

We defined treatment nonadherence as an imperfect correspondence between the intended course of randomly assigned treatment and the actual treatment received [1]. We distinguished between studies of interventions typically intended to be "one-off" in nature (e.g., surgery) and those typically intended to be "recurring" (such as behavioral therapy sessions or a course of pharmacotherapy). For all studies, we attempted to ascertain from trial reports the number of participants who received some of their randomly allocated treatment (i.e., "initiated"). For "recurring" interventions, we also extracted information on the number of participants who adhered to their intended course of treatment ("completed") and a measure of treatment "intensity" (such as the number of sessions or prescriptions taken). It is common for the intended frequency or duration of treatment to be patient specific (27 trials, 28%), particularly in trials with a recurring intervention in which personalized dose titration or stepped care is used. In such studies, it may be impossible to calculate how many patients "completed" their intended course of treatment; nonetheless, we estimated the proportion of all trials that reported treatment "initiation," "completion," and "intensity."

Definition of the Analysis Set

We recorded the type of analysis used in the primary economic evaluation based on the information provided (e.g., CONSORT diagrams) or the author's own definition. Studies analyzed participants in the treatment group they were randomized to ("analyzed as randomized") or according to the treatment they actually received ("analyzed as treated"). For those who were analyzed as randomized, we also recorded whether all randomized participants were included in the analysis ("strict ITT"). Studies often do not include all participants in the analysis—for example, excluding those who withdrew or with no follow-up data ("complete case" analysis). In addition, "per-protocol"analyses exclude participants violating the protocol, for example, participants not completing treatment or not meeting inclusion criteria.

Methods for Costing the Interventions

For studies that reported nonadherence or a measure of treatment intensity, we extracted information about the methods used for calculating intervention costs, provided this was reported in sufficient detail.

We categorized each component of the intervention costs on the basis of three criteria (Table 1): 1) Type of cost (fixed/semi-fixed/variable) [8]; 2) the method for assigning shared costs to participants (indirect/direct); and 3) where applicable, units used for estimating variable costs for individuals. This allowed us to assess the consistency of costing methods used in trials with nonadherence.

We also recorded information on any statistical methods, beyond an as-treated or per-protocol analysis, to estimate the cost-effectiveness of an intervention in those able to adhere to it.

Results

Our search identified 330 articles; 97 (29%) articles, reporting on 96 unique RCTs, satisfied the eligibility criteria (Fig. 1; see full list of articles in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.07.009).

For 57 (59%) trials, the primary economic evaluation was a cost-effectiveness or cost-utility analysis, whereas in 37 (39%) it was a cost-consequence analysis, in 1 (1%) a cost-benefit analysis, and in 1 (1%) a cost-minimization analysis. Interventions evaluated included 20 (21%) pharmacological, 25 (26%) surgical, 9 (9%) diagnostic, 15 (16%) behavioral/psychosocial/educational, and