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Different methods of allocation to groups in randomized trials are associated with different levels of bias. A meta-epidemiological study

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Abstract

Objective: Insecure hiding of the treatment allocation in randomized trials is associated with bias. It is less certain how much bias is associated with different methods of treatment allocation.

Study Design and Setting: Meta-epidemiological study of 389 randomized trials from 19 systematic reviews and 65 meta-analyses with differing methods of treatment allocation. Pooled ratios of odds ratios (RORs) and 95% confidence intervals (95% CI) were calculated from trials with different methods of treatment allocation. An ROR less than one shows exaggeration of treatment effect.

Results: There is no evidence that the use of sealed envelopes with enhancement was different from central randomization (ROR 1.02, 95% CI: 0.85−1.23). Sealed envelopes without enhancement were associated with an exaggeration of the estimate of effect (ROR 0.87, 95% CI: 0.76−1.00). Where allocation concealment for double-blind trials was unclear, the ROR is 0.86 (95% CI: 0.78−0.96) and if not hidden, the ROR is 0.89 (95% CI: 0.70−1.15).

Conclusion: Sealed envelopes with some form of enhancement (opaque, sequentially numbered, and so forth) may give adequate concealment. Description of a study as "double blind" does not imply a lack of bias when concealment of allocation is unclear.

Keywords: Allocation concealment; Bias; Meta-epidemiology; Blinding; Randomized trials; Meta-analysis

1. Introduction

Although the best evidence of the effect of medical interventions comes from systematic reviews and meta-analyses of randomized trials, these are potentially subject to bias. Often these biases are associated with how trials are carried out. A number of methodological studies have examined the method of allocation to groups and have found empirical evidence of bias [1−6]. Meta-analysis of these methodological studies [7−9] indicates that this bias results in an overestimate of treatment effect of around 20% for studies with inadequate allocation concealment compared with those that have more secure methods of concealing the allocation. In another study, which reported data from 499 trials included in 70 meta-analyses [10], two-thirds of conclusions in favor of one of the interventions were no longer supported if only trials with adequate allocation concealment were included in the meta-analysis. The amount of bias associated with allocation concealment may also depend on the outcome, with objective outcomes being associated with less bias than subjective outcomes [11].

Previous studies examining bias associated with allocation concealment mostly coded the method of group allocation as hidden and unclear [2−6], or in one case, hidden, unclear, and not hidden [1]. However, there are many ways of allocating participants to groups, ranging from those that are more securely hidden, such as a third party Web site or telephone access or allocation of numbered prepacked medications or identical placebos by a pharmacy (central randomization), to those that are clearly not hidden, such as whether the participants date of birth is odd or even. Between central randomization and the clearly not hidden lies other methods, which may be somewhat insecure. Reporting of allocation concealment is often insufficient to make a clear judgment. This study explores, at a finer level of detail than has been done previously, the methods of group allocation in individual trials and the associated biases.

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What is new?

Key findings:
Inadequate concealment of allocation can lead to exaggeration of treatment effects in randomized controlled trials. Many methods of allocation to groups are used, and it is not clear which provide adequate concealment. This study provides estimates of the degree of exaggeration associated with different allocation methods.

What this adds:
Sealed envelopes with extra security features appear to provide adequate concealment. Saying only that a study is double blind is not sufficient to ensure lack of exaggeration of effect.

Implications:
If it is not possible to use a truly secure method of allocation, then sealed, opaque, sequentially numbered envelopes may provide adequate allocation concealment.

2. Methods

Full details of the methods of data collection were reported previously [12]. Briefly, systematic reviews in issue 1, 2001 of the Cochrane Library were searched for binary outcomes that had at least 10 included trials, at least one of which had more than 500 people randomized to each arm. For these outcomes, the report of the contributing trials was found, and the data were extracted in duplicate by two trained research assistants. The results for the binary outcomes were taken from the Cochrane Review as the total number and number positive for each arm in the study.

Each included trial was coded for the method of allocation into one of six categories. Category 1 comprised trials that used some form of central randomization that clearly should hide the allocation, such as a remote telephone service or randomization by a pharmacy. Category 2 comprised trials that used sealed envelopes with some form of security enhancement, such as ensuring that envelopes were opaque and numbered. Category 3 comprised trials that used sealed envelopes without any further details. Category 4 comprised trials that were reported as randomized without details, and also as "double blind." Category 5 comprised trials that simply said they were randomized with no further details. Category 6 comprised trials where the allocation was clearly not hidden, for example, being based on an open list, odd or even days of the week, participant's birth date, or the team on duty at enrollment. Categorization into one of these six groups was conducted independently by two people, with discussion with a third person to resolve any disagreements.

To facilitate comparison with previous meta-analyses, these six categories were combined to create two groups: an "adequate concealment" group combining groups 1 and 2 and the remainder to form an "inadequate or unclear concealment" group.

Analysis was done in Stata V10 (StataCorp, College Station, TX) using the meta-epidemiology approach described by Sterne et al. [13]. Odds ratios (ORs) and their standard errors were calculated from the appropriate two by two tables using the metan routine in Stata [14]. This was used as metan adds variables for the natural log of the OR and its standard error to the file. This process was not used to produce pooled results. Then random-effects meta-regression was used on each meta-analysis using the method of allocation as the covariate [15]. The central randomization group was used as the reference group for the six-group comparison, and "adequate concealment" was used for the two-group comparison. The coefficients in the meta-regression give ratios of ORs (RORs), which were themselves combined using metan with random effects to give pooled RORs with 95% confidence intervals (95% CIs). The data from the meta-analyses were not independent as more than one meta-analysis from a systematic review was included. These often contained the same studies. To allow for this, the meta-analysis of the RORs was bootstrapped to get bootstrap CIs with one meta-analysis being chosen at random from each systematic review, and the results were analyzed. This was repeated 1,000 times. Because of the results of this analysis, a post hoc comparison between security-enhanced envelopes and envelopes without enhancement was carried out.

Calculations were always done so that ORs less than one indicated beneficial effects of the treatment. This implies that an exaggeration of the treatment effect would lead to an ROR less than one. The pooled ROR for the two-category result (adequate/not adequate) was added to the meta-analysis of similar studies reported by Jüni et al. [7] and then Egger and Ebrahim [8] and since updated by Gluud [9] but with the correction from Kjaergard et al. [16]. Random-effects meta-analysis was used for this calculation.

3. Results

The search identified 67 meta-analyses from 19 systematic reviews. Two of these, from the same systematic review, had to be discarded as too many of the studies had zero events in both arms. The remaining 65 meta-analyses from 18 systematic reviews included 389 studies. Details of the systematic reviews and outcomes are given in Table 1. The number of studies in individual meta-analyses ranged from 10 to 63. Sixty-seven studies used central randomization (category 1), 18 used enhanced envelopes (category 2), 48 envelopes with no further details (category 3), 121 reported that they were double blind but had unclear allocation