Of these, 41 were excluded (non-ICU studies, 20; repeated data from previous studies, 10; use of active controls, 8; nontherapeutic study, 3). Placebo disclosure was evident in only 62% of the 146 studies, with a significantly higher disclosure rate in trials involving parenteral administration of the trial drug as compared with enteral (68% vs. 41%, $P < 0.01$). No statistically significant difference in disclosure rate could be identified with respect to adult versus pediatric ($P = 0.28$), journal impact factor ($P = 0.47$), single versus multi-center ($P = 1.0$), registered versus unregistered ($P = 0.27$), phase of trial ($P = 0.78$), or pharmaceutical sponsorship ($P = 0.49$). As compared with trials in the general medical population, there was a significantly higher disclosure rate in the critical care literature (62% vs. 17%, $P < 0.0001$) (1). A list of the various trials reviewed in this study can be found in the online supplement.

In the past decade, several standards have been developed for reporting of RCTs (3–5) that mandate that “Authors should describe each intervention thoroughly, including control interventions” (5) to make reporting complete, transparent, and reproducible. The journals included in our study instruct authors to adhere to these guidelines. Despite these, we did not find any difference in disclosure rates irrespective of trial registration or the journal impact factor. The reasons for the incomplete disclosure of placebos may relate to the difficulties in manufacturing a perfectly matched placebo, and potential concerns about the possible or negative effects of placebo. Of note, pharmaceutical sponsored trials (implying greater manufacturing support) also suffered from limited disclosure rates. The higher disclosure rate in the critical care as compared with the general medical population may be related to the higher number of studies with parenteral preparation (77% vs. 46%, $P < 0.0001$). The results of the study clearly suggest that in a third of the trials, the patient may not know what he or she is receiving, and the placebo could have an interaction with the patient’s illness that the reviewers and the readers may not be aware of.

In conclusion, otherwise well-designed randomized controlled trials in critically ill patients fail to consistently report placebo content. The reporting of placebo composition needs significant improvement, and despite several guidelines for authors it probably rests on combined effort from researchers, publishers, and sponsors to achieve this goal.

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Time until Relapse in Tuberculosis Treatment Trials: Implication for Phase 3 Trial Design

To the Editor:

The number of new drugs and combinations for tuberculosis treatment that require testing has increased during the past 5 years; however, the number of trial sites in high-burden countries capable of conducting registration-quality trials is limited. The primary endpoint for response to treatment in most earlier phase 3 trials was relapse at least 24 months after completion of therapy. Coupled with the large number of patients required and the challenge of following up patients in resource-constrained settings, the long length of follow-up has meant that such trials require upwards of 5 years to enroll and complete. If the length of follow-up could be shortened without missing a substantial number of relapses, the time and resources necessary to complete such trials could be reduced.

Investigators have reexamined the timing of relapse in earlier studies to inform regulatory authorities and guide the design of future trials. In a reanalysis of trials conducted from 1970 to 1983 by the British Medical Research Council, 78% of relapses occurred within 6 months of stopping treatment and 91% occurred within 12 months (1). To add to this information, we examined data from a recent phase 3 randomized trial of shortening treatment from 6 to 4 months in adults with drug-susceptible tuberculosis (TB) done in Brazil, Uganda, and the Philippines (2). Subjects were followed with sputum cultures monthly during treatment and every 3 months thereafter for a total of 30 months after beginning treatment. Eighteen of 370 patients developed recurrent TB. Two recurrences due to exogenous reinfection were excluded. The mean time after treatment until relapse was 7 ± 4.4 months. Of the 16 relapses, 11 (69%) occurred within the first 6 months after stopping treatment, 13 (81%) occurred within 12 months, and 15 (94%) occurred within 18 months. The timing of relapse did not differ between sites. Our results support reconsideration of the follow-up time required after treatment in phase 3 registration trials of new TB drugs and regimens for drug-susceptible TB.

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