Item 6b. Any changes to trial outcomes after the trial commenced, with reasons

Example—“The original primary endpoint was all-cause mortality, but, during a masked analysis, the data and safety monitoring board noted that overall mortality was lower than had been predicted and that the study could not be completed with the sample size and power originally planned. The steering committee therefore decided to adopt co-primary endpoints of all-cause mortality (the original primary endpoint), together with all-cause mortality or cardiovascular hospital admissions (the first pre‑ specified secondary endpoint).”

Explanation—There are many reasons for departures from the initial study protocol (see item 24). Authors should report all major changes to the protocol, including unplanned changes to eligibility criteria, interventions, examinations, data collection, methods of analysis, and outcomes. Such information is not always reported. As indicated earlier (see item 6a), most trials record multiple outcomes, with the risk that results will be reported for only a selected subset (see item 17). Pre-specification and reporting of primary and secondary outcomes (see item 6a) should remove such a risk. In some trials, however, circumstances require a change in the way an outcome is assessed or even, as in the example above, a switch to a different outcome. For example, there may be external evidence from other trials or systematic reviews suggesting the end point might not be appropriate, or recruitment or the overall event rate in the trial may be lower than expected. Changing an end point based on unblinded data is much more problematic, although it may be specified in the con‑ text of an adaptive trial design. Authors should identify and explain any such changes. Likewise, any changes after the trial began of the designation of outcomes as primary or secondary should be reported and explained. A comparison of protocols and publications of 102 randomised trials found that 62% of trials reports had at least one primary outcome that was changed, introduced, or omitted compared with the protocol. Primary outcomes also differed between protocols and publications for 40% of a cohort of 48 trials funded by the Canadian Institutes of Health Research. Not one of the subsequent 150 trial reports mentioned, let alone explained, changes from the protocol. Similar results from other studies have been reported recently in a systematic review of empirical studies examining outcome reporting bias.