Item 3b. Important changes to methods after trial commencement (such as eligibility criteria), with reasons

Example—“Patients were randomly assigned to one of six parallel groups, initially in 1:1:1:1:1:1 ratio, to receive either one of five otamixaban … regimens … or an active control of unfractionated heparin … an independent Data Monitoring Committee reviewed unblinded data for patient safety; no interim analyses for efficacy or futility were done. During the trial, this committee recommended that the group receiving the lowest dose of otamixaban (0·035 mg/kg/h) be discontinued because of clinical evidence of inadequate anticoagulation. The protocol was immediately amended in accordance with that recommendation, and participants were subsequently randomly assigned in 2:2:2:2:1 ratio to the remaining otamixaban and control groups, respectively.”

Explanation—A few trials may start without any fixed plan (that is, are entirely exploratory), but the most will have a protocol that specifies in great detail how the trial will be conducted. There may be deviations from the original protocol, as it is impossible to predict every possible change in circumstances during the course of a trial. Some trials will therefore have important changes to the methods after trial commencement. Changes could be due to external information becoming available from other studies, or internal financial difficulties, or could be due to a disappointing recruitment rate. Such protocol changes should be made without breaking the blinding on the accumulating data on participants’ outcomes. In some trials, an independent data monitoring committee will have as part of its remit the possibility of recommending protocol changes based on seeing unblinded data. Such changes might affect the study methods (such as changes to treatment regimens, eligibility criteria, randomisation ratio, or duration of follow-up) or trial conduct (such as dropping a centre with poor data quality). Some trials are set up with a formal “adaptive” design. There is no universally accepted definition of these designs, but a working definition might be “a multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial.” The modifications are usually to the sample sizes and the number of treatment arms and can lead to decisions being made more quickly and with more efficient use of resources. There are, however, important ethical, statistical, and practical issues in considering such a design. Whether the modifications are explicitly part of the trial design or in response to changing circumstances, it is essential that they are fully reported to help the reader interpret the results. Changes from protocols are not currently well reported. A review of comparisons with proto‑ cols showed that about half of journal articles describing RCTs had an unexplained discrepancy in the primary out‑ comes. Frequent unexplained discrepancies have also been observed for details of randomisation, blinding, and statistical analyses