Item 9. Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned

Examples—“The doxycycline and placebo were in capsule form and identical in appearance. They were prepacked in bottles and consecutively numbered for each woman according to the randomisation schedule. Each woman was assigned an order number and received the capsules in the corresponding prepacked bottle.”

“The allocation sequence was concealed from the researcher (JR) enrolling and assessing participants in sequentially numbered, opaque, sealed and stapled envelopes. Aluminium foil inside the envelope was used to render the envelope impermeable to intense light. To prevent subversion of the allocation sequence, the name and date of birth of the participant was written on the envelope and a video tape made of the sealed envelope with participant details visible. Carbon paper inside the envelope transferred the information onto the allocation card inside the envelope and a second researcher (CC) later viewed video tapes to ensure envelopes were still sealed when participants’ names were written on them. Corresponding envelopes were opened only after the enrolled participants completed all baseline assessments and it was time to allocate the intervention.”

Explanation—Item 8a discussed generation of an unpredictable sequence of assignments. Of considerable importance is how this sequence is applied when participants are enrolled into the trial (see box 1). A generated allocation schedule should be implemented by using allocation concealment, a critical mechanism that prevents foreknowledge of treatment assignment and thus shields those who enroll participants from being influenced by this knowledge. The decision to accept or reject a participant should be made, and informed consent should be obtained from the participant, in ignorance of the next assignment in the sequence. The allocation concealment should not be confused with blinding (see item 11). Allocation concealment seeks to prevent selection bias, protects the assignment sequence until allocation, and can always be successfully implemented. In contrast, blinding seeks to prevent performance and ascertainment bias, protects the sequence after allocation, and cannot always be implemented. Without adequate allocation concealment, however, even random, unpredictable assignment sequences can be subverted. Centralised or “third-party” assignment is especially desirable. Many good allocation concealment mechanisms incorporate external involvement. Use of a pharmacy or central telephone randomisation system are two common techniques. Automated assignment systems are likely to become more common. When external involvement is not feasible, an excellent method of allocation concealment is the use of numbered containers. The interventions (often drugs) are sealed in sequentially numbered identical containers according to the allocation sequence. Enclosing assignments in sequentially numbered, opaque, sealed envelopes can be a good allocation concealment mechanism if it is developed and monitored diligently. This method can be corrupted, however, particularly if it is poorly executed. Investigators should ensure that the envelopes are opaque when held to the light, and opened sequentially and only after the participant’s name and other details are written on the appropriate envelope. A number of methodological studies provide empirical evidence to support these precautions. Trials in which the allocation sequence had been inadequately or unclearly concealed yielded larger estimates of treatment effects than did trials in which authors reported adequate allocation concealment. These findings provide strong empirical evidence that inadequate allocation concealment contributes to bias in estimating treatment effects. Despite the importance of the mechanism of allocation concealment, published reports often omit such details. The mechanism used to allocate interventions was omitted in reports of 89% of trials in rheumatoid arthritis, 48% of trials in obstetrics and gynaecology journals, and 44% of trials in general medical journals. In a more broadly representative sample of all randomised trials indexed on PubMed, only 18% reported any allocation concealment mechanism, but some of those reported mechanisms were inadequate.