

Don't Cherry-Pick Study Subjects

By Paul Latimer

The eligibility (inclusion/exclusion) criteria for a study protocol should be carefully designed to ensure meaningful results and subject safety. Studies with loose eligibility criteria are relatively easy to enroll and represent the clinical population, but may require larger samples to offset the variability in the study population. Studies with tight eligibility criteria require smaller samples because of the uniformity of the study population, but are relatively hard to enroll and may not represent the clinical population for which the study treatment is intended.

No matter what the eligibility criteria, it is essential that the investigator abide by them. Deviations from the eligibility criteria are protocol violations, with potentially serious ramifications for the study and investigator. While most protocol violations are due to oversight or ignorance, deliberate violations are very serious matters that constitute breaches of the clinical trial agreement and FDA Form 1572 – Statement of Investigator.

Cherry-picking subjects based on the severity of their illness, comorbidities, health insurance, or other parameters can bias the results and even invalidate the study. It is common for inexperienced investigators to ask sponsors to make small exceptions (e.g., if a subject is just a week over the upper age limit), but experienced sponsors refuse such requests because they create data analysis and other problems. A lecture on the sanctity of the protocol may be forthcoming. Once you start allowing such exceptions, where do you draw the line? How do you do it consistently?

With "flexible" eligibility criteria, the study's population may not be representative, the results can be misleading, the study cannot be replicated, there might be safety issues, and the results could even be manipulated.

The above facts and issues are well known, so it is shocking to investigators — or should be — when it is the study sponsor cherry-picking the subjects. In the author's experience, when this happens, the sponsor is not including ineligible subjects; instead, it is excluding, or attempting to exclude, eligible subjects. There is a simple, albeit expensive and time-consuming remedy: amending the protocol. Even better, the protocol could be written correctly in the first place. In any case, there is no excuse for a sponsor to cherry-pick subjects; it is a clear and deliberate protocol violation.

Examples

The following are some examples from the author's experience over the past six months. All occurred with mid- to large-sized pharmaceutical companies over the investigator's objections.

Example 1. Neuropathic pain study

This study included the exclusion criterion: "History of alcohol and/or drug abuse in the investigator's judgment, based on subject history and physical examination." The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV/MINI) includes a clear and widely accepted definition of the term "abuse" in the context of alcohol and/or drug abuse. To be considered abuse, one of the following must be present as per the MINI (Mini International Neuropsychiatric Interview):

- Intoxicated, high or hung-over more than once when they had other responsibilities at school, at work, or at home
- Intoxicated more than once in any situation where they were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.
- Legal problems more than once because of their drinking or drug use, for example, an arrest for disorderly conduct
- Continuing to drink or use drugs even though their drinking or drug use caused problems with their family or other people.

The sponsor expelled a subject from the study when he had a positive urine test for cannabis. "Abuse" and "use" are not equivalent. The subject passed the Mini International Neuropsychiatric Interview administered in the screening process and did not come close to meeting the DSM definition of drug abuse. There was no exclusion criterion about a positive test for cannabis. Furthermore, the protocol specifically stated that eligibility decisions were "in the investigator's judgment," i.e., not the sponsor's.

In our experience, it is fairly common for sponsors to exclude potential subjects for casual drug use contrary to the protocol. For example, in another study, the sponsor excluded a potential subject for recreational drug use (infrequent cannabis and ecstasy), even though he passed the Mini International Neuropsychiatric Interview per the protocol.

Example 2. Depression with pain study

This study evaluated the effect of an antidepressant on pain that arose during the depression and was not due to some other primary cause. As we got underway, the sponsor started expelling eligible subjects who had any other diagnostic labels attached to the pain, even if those labels were incorrect or secondary. The family physicians that referred potential subjects to our site customarily attribute pain not to depression but to some other cause like irritable bowel syndrome, fibromyalgia or arthritis. For example, if a depressed patient complains of joint pain for the first time during their depression, the diagnosis might be osteoarthritis, even though their joints are no different than they were before the depression. Very often, such pain resolves when the depression resolves. Similarly, it is not unusual for depressed patients to develop constipation and abdominal pain during their depression, which resolve when the depression resolves. Nevertheless, family physicians almost never attribute pain to depression. Once an incorrect diagnosis was in a patient's medical chart, however, we were not permitted to correct the primary cause to depression, no matter how clear the situation. What started out as a clinically interesting study with easy enrollment became medically meaningless and almost impossible to enroll. We withdrew from the study

Example 3. Depression study

In this study, we were directed to exclude "major/unstable medical problems that, in the investigator's judgment, might substantially increase the risk to the subject." This is a fairly standard exclusion criterion. In this example, the site monitor overruled the investigator on a subject who had multiple medical conditions that were not major or unstable individually or collectively. The medical monitor overruled the site monitor, who should have referred the question to the medical monitor in the first place. Higher powers then overruled the medical monitor. Although we were not informed of the rationale, the sponsor required us to expel the subject from the study.

Example 4. Bipolar depression study

We were very excited about this study and the investigational compound. We had many bipolar patients who would meet the stated criteria. Everything went well until we informed

the sponsor that we had screened our first subject. We then learned that the sponsor required a pre-enrollment telephone conference about each prospective subject, to review his or her clinical history in detail and decide whether the subject was suitable. Even if a subject met all the eligibility criteria, he or she could still be excluded if the sponsor team (senior CRA and site monitor) decided he or she was not a "good" subject based on undefined criteria. We withdrew from this study immediately.

Conclusion

Investigators should know better than to cherry-pick subjects. Those who do it consciously are probably discrete about it. In contrast, when sponsors cherry-pick subjects, it is no secret to the investigator. If sponsors want to handpick the best subjects for a study, they should say so in the protocol, a humorous scenario at best. The above examples appear to be deliberate protocol violations. They may be due to stunning ignorance, but all sponsor personnel involved appeared to be experienced. This kind of meddling with the conduct of a clinical trial may go unnoticed by auditors and FDA investigators. The FDA may not glean it from the New Drug Application. In the author's opinion, investigators should report such incidents to their IRB as protocol violations, and the IRB should have a very serious discussion with the sponsor.

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