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Even More Regulatory Myths in Clinical Research

By Parker Nolen

"Beware of false knowledge. It is more dangerous than ignorance."

– George Bernard Shaw

Introduction

The regulations set a floor on the standards by which we conduct clinical research. We are free to set higher standards, but undershooting regulatory requirements constitutes noncompliance and overshooting them can waste time and perhaps interfere with legitimate research. Operating on a false understanding of the requirements is a recipe for trouble.

Two previous articles ("Regulatory Myths in Clinical Research," September 2014, and "More Regulatory Myths in Clinical Research," May 2015) tested your knowledge of regulatory requirements. This article will further test your knowledge. *Caveat lector*: Some of the statements below are tricky, so read them very carefully.

A retrospective chart review that records identifiers might be considered exempt from IRB review.

TRUE. The following research activities are exempt from IRB review: "Research involving the collection or study of existing data,…if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects." (46 CFR 46.101(b)(4)) You may indeed have a study that qualifies for exempt status, even if identifiers are recorded. The key question is whether or not a study participant can be identified from the information collected.

Assent must be documented with an assent form.

FALSE. The regulations state, "When the IRB determines that assent is required, it must also determine whether and how assent must be documented" (21 CFR 50.55(g)) In other words, the regulations leave it to the IRB to decide how assent will be documented, important flexibility when young children are involved.

An investigator can enroll an ineligible participant if the sponsor grants a waiver.

FALSE. The regulations state, "[E]ach IRB shall: Follow written procedures… for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval..." (21 CFR 56.108) In other words, IRB approval is required before enrolling an ineligible participant, and should be granted if it does not put the person's safety or welfare at undue risk or significantly compromise the scientific merit of the study.

A participant who becomes incarcerated must be dropped from the research if the research has not been reviewed under Subpart C

TRUE, mostly. 45 CFR 46 Subpart C (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) sets forth additional protections for IRB review of research involving prisoners. In the absence of these protections, the incarcerated participant must be dropped from the study. (Think about the logistics of follow-up visits and handling adverse events.)

"OHRP allows one important exception to the requirement that all research interactions or interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the regulatory requirements for research involving prisoners are met. In special circumstances in which the investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the subject may continue to participate in the research until the requirements of subpart C are satisfied. The investigator must promptly notify the IRB of this occurrence, so that the IRB can re-review the study." (OHRP Prisoner Research FAQs)

Your IRB can review research involving prisoners without a prisoner representative on the board.

TRUE, sort of. The regulations state, "At least one member of the Board shall be a prisoner or a prisoner representative… except that, where a particular research project is reviewed by more than one Board, only one Board need satisfy this requirement" (45 CFR 46.304(b)) In other words, if another IRB with a prisoner representative has reviewed the research, whether or not it approved the research, your IRB does not need to have a prisoner representative.

Prisoner research requires a full-board review.

FALSE. Although OHRP prefers a full-board review, the regulations are silent on the level of review required. The guidance states, "because of the vulnerability of prisoners, OHRP recommends that all research involving prisoners be reviewed by the convened IRB. If the research is reviewed under the expedited review procedure, OHRP recommends that the IRB member(s) reviewing the research include a prisoner or prisoner representative." (OHRP "Prisoner Research FAQs")

If a participant takes an aspirin while he happens to be on a research study and then sprains his wrist, it is an adverse event.

TRUE. The regulations state, "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." (21 CFR 312.32(a)) "Associated with" means concurrent in time. "Drug related" means there is a causal relationship. Perhaps the aspirin worked so well that the participant overdid a physical activity. Even the injuries from getting hit by a meteor count as an adverse event.

Investigators must report "adverse events" to the IRB.

FALSE, sort of. Although the term "adverse event" does not even appear in 21 CFR 50, 56 or in 45 CFR 46, there *is* a requirement to report "averse events" in 21 CFR 312 and 21 CFR 812, so don't try using the regulatory wording as an excuse.

Investigators must report protocol deviations to the IRB.

FALSE, sort of. The term "protocol deviation" does not appear in 21 CFR 50, 21 CFR 56, 45 CFR 46, 21 CFR 312, or 21 CFR 812. However, your IRB must be able to oversee the conduct of your clinical study, so it will probably insist that you report protocol deviations to it.

Consent forms must disclose the procedures used to maintain confidentiality.

FALSE. The regulations state, "In seeking informed consent, the following information shall be provided to each subject:… A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained..." (21 CFR 50.25(a)). In other words, the consent form could merely say, "We will consider the following information confidential…" It does not have to set forth the procedures for confidentiality, but the IRB will probably want a more detailed explanation for its own use.

If the FDA were to conduct human subjects research it must follow 21 CFR 50 and 56.

FALSE. The FDA is part of HHS, so its research is governed by the Common Rule (45 CFR 46). However, the conduct of the research should be in accordance with 21 CFR 312 and 21 CFR 812, if applicable.

Expedited means fast.

TRUE, sort of. Definitions: "1: to execute promptly; 2: to accelerate the process or progress of: speed up; 3: issue, dispatch" (www.Miriam-Webster.com) Of course, your idea of "fast" might differ from that of your IRB.

Conclusion

The clinical research enterprise has enough challenges without having to wrestle with regulatory requirements that do not exist. Many of the regulations are deliberately vague and general, to cover unanticipated scenarios and discourage the use of possible loopholes. Interpretation is thus often necessary.

If anyone tells you the regulations require you to do something that will be burdensome or doesn't sound quite right, pull a Jerry McGuire and say, "Show me the regs." That might just be the last you hear about that requirement. There's nothing wrong with asking, "Why?" Just don't be a jerk about it.

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