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More Regulatory Myths in Clinical Research

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"Let me tell you a true story…or at least it should be true…"

– Cedric The Entertainer

Introduction

As stated in a previous article ("Regulatory Myths in Clinical Research," September 2014, http://firstclinical.com/journal/2014/1409_Myths.pdf), the regulatory complexity of clinical research is legendary. Adding to the complexity are numerous regulatory myths, presumed rules that emerged from a standard operating procedure, "best practice," misunderstanding, assumption, rationalization or good intention. If something sounds like it should be a regulation, what's the harm in playing it safe? Well, complying with mythical regulations is a time-consuming distraction that might even lead to non-compliance with real regulations.

As in the previous article, test your knowledge about which of the following requirements are regulation or myth.

Informed consent forms (ICFs) must be written at an eighth-grade reading level.

FALSE. There are no regulations requiring a specific reading level, only that "information that is given to the subject or the representative shall be in language understandable to the subject or the representative." (21 CFR 50.20 and 45 CFR 46.116)

In 2014, the FDA issued guidance on readability in consent forms ("Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors" at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf). This document includes the statement that "Consent forms that are long, complex, legalistic and have a high reading level may overwhelm potential subjects and may inhibit reading of the full document and understanding of the relevant information." The document cites the recommendation of a working group formed by the National Cancer Institute (NCI) and the Office for Protection from Research Risks (now the Office of Human Research Protections, OHRP) that consent forms be written at an eighth-grade or lower reading level ("Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials.") That's the closest FDA gets to recommending an eighth-grade reading level.

However, some federal agencies and institutions, notably other divisions of NIH, recommend consent-form reading levels. For example, the National Heart Blood and Lung Institute (NHLBI) says, "Most IRBs will request that Informed Consent forms be written at a sixth- to eighth-grade reading level." (http://www.nhlbi.nih.gov/research/funding/research-support/crg/funding/consent-forms.htm). A cautious investigator might go with this guideline. After all, if you want NHLBI funding, you should probably abide by their recommendations. However, writing a consent form at the eight-grade level is much easier said than done, and manipulating the text to reduce the reading level score can actually decrease comprehensibility.

ORHP guidance for research conducted or supported by HHS, "IRB Approval of Research with Conditions" includes the following illustration of an IRB's possible requirement for conditional approval:

Requiring simplification of the description of the study risks in the informed consent document to be at an eighth-grade comprehension level, and designating the IRB chairperson to review the revised informed consent document and ensure that risks are accurately described and understandable at an eighth-grade comprehension level.

In other words, an IRB might, based on its own judgment, for certain studies, require an eighth-grade reading level.

However, an adult clinical trial consent form written at the eighth-grade level is a rare flower. This article achieves a Flesch-Kincaid Grade Score of 12.2, so you have to ask yourself, "Does this article seem easier or harder to read than your typical consent form?"

When a new version of an ICF is released, currently enrolled participants must be re-consented.

FALSE, as a blanket rule. Currently enrolled participants that are affected by the change must be re-consented. For example, if a new risk has been observed, currently enrolled participants must be re-consented, provided that risk is relevant to them. But, for example, if that new risk has already passed without incident, re-consent is not required. The IRB might also conclude that a new risk, e.g., "redness at the injection site," is too trivial to justify re-consenting. Administrative changes generally do not require re-consenting.

Notes to File are required by the FDA or ICH GCP.

FALSE. A note to file can document or clarify unusual (but not reportable) occurrences or repeated issues and a site's corrective actions, but the words "note to file" (NTF) or "memo to file" do not exist in any guidelines, to say nothing of any regulations.

For review and approval of clinical trials, the IRB Chair must be a licensed physician or healthcare provider.

FALSE. No regulation specifies any professional licensing or credentials for the IRB Chair, or anyone else on the IRB for that matter. There is just the collective requirement that "the IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects." (45 CFR 46.107 and 21 CFR 56.107). Oddly, the objective of this regulation is to "promote respect for [the IRB's] advice and counsel," not for the IRB to actually make better decisions.

In a protocol study review under 45 CFR 46 Subpart C (research involving prisoners), IRB approval is contingent on the prisoner representative on the IRB voting to approve the study.

FALSE. The regulations specify that, for studies involving prisoners, "at least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, 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, like any other member of the IRB, the "prisoner rep" has a vote, but not a veto.

The IRB must notify the principal investigator that approval will expire within 30 days.

FALSE. It sounds like a good idea, but it is not a regulatory requirement.

If IRB approval expires, it must be reported to the FDA and/or OHRP.

FALSE. The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval before the previous approval expires does not automatically require a suspension or termination of IRB approval. However, the IRB has the discretion to suspend or terminate a study for that reason. 21 CFR 56.113 and 45 CFR 46.113 state:

> IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements... Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

The IRB should determine the reasons for the non-compliance and take appropriate corrective actions. (FDA "Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval")

The IRB Chair must sign correspondence associated with IRB votes and determinations.

FALSE. There is no regulation requiring signatures by the IRB Chair, only a requirement that the IRB maintain adequate records, have and follow written procedures, and provide written communications and summaries as needed. (21 CFR 56.115 and 45 CFR 46.115). Each institution may develop its own rules for who is authorized to sign what.

FDA regulations specify that only the IRB Chair can approve a protocol under Expedited Review.

FALSE. 21 CFR 56.110 and 45 CFR 46.110 state:

> Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB.

The IRB must evaluate risks associated with standard-of-care procedures specified in the protocol.

TRUE, for risks to study participants. If it's in the protocol, it's a research risk. Standard of care varies from region to region, institution to institution, physician to physician, and patient to patient. Absent the study, a patient might decline standard-of-care treatment. In assessing risk vs. benefit, the IRB must even evaluate risks associated with alternate treatments if the patient does not participate in the study.

For pediatric studies, the IRB is responsible for verifying that principal investigators and other research personnel having regular contact with study participants pass a criminal background check.

FALSE. There are no such requirements in the regulations. Under 45 CFR 46.111 and 21 CFR 56.111, the IRB has the right to perform such checks or request them from the Human Resources, Institutional Risk Management, or Security department. However, it seems like overkill except when there are specific concerns.

During an FDA site visit of an IRB, only the Institutional Official need be available for questions and information. The IRB Chair is not involved in such a site visit.

DEPENDS. FDA IRB site visits (the routine type) are intended to assess and evaluate actions and operations of the IRB engaged in review and oversight of FDA relevant research. To

that end, such site visitors (investigators) inform and interact with "the most responsible IRB representative," usually the IRB Chair (Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Institutional Review Board Inspections).

The bulk of the visit is to "interview appropriate people and obtain information about the IRB's policies and procedures." Usually, the IRB's performance is evaluated by tracking one or more studies that are subject to IRB review under FDA regulations. Also, the IRB's procedures and membership rosters are examined to determine whether they conform to current FDA regulations. The Institutional Official might wish to be involved in such information exchanges and interactions but usually only attends the exit interview.

Of course, in the event that deficiencies are found, the FDA inspection will result in a written Form FDA 483 letter to "the most responsible IRB representative," usually the Institutional Official. At this point, it is likely that lots of people associated with the IRB will get involved…but that's a story for another day.

Conclusion

So, how can we stop regulatory myths from spreading? To start with, we all need to be familiar with the regulations and guidances. When in doubt, look it up. Let's not say something is a regulatory requirement unless it really is. If an IRB administrator, site monitor, auditor, or FDA investigator says something is a regulatory requirement, give it the smell test; don't just take their word for it. Ask for the citation or even a written explanation. Remember, 21 CFR 56.109(e) and 45 CFR 56.109(e) state:

> If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

And, lastly, help identify other regulatory myths. Please send in your examples for the next incarnation of this article. Or, if one of the rules categorized above as a myth is not actually a myth, please explain. Credit (if requested) will be given where due for any suggestions or recommendations.

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