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Regulatory Myths in Clinical Research

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> "What gets us into trouble is not what we don't know. It's what we know for sure that just ain't so.
>
> – Mark Twain

Introduction

The regulatory complexity of clinical research is legendary. But, on top of all these rules, there are mythical requirements that burden the process but don't actually exist. How did this happen? Perhaps, over time, people just *assumed* that a "best practice" or policy was a regulatory requirement. Perhaps a site monitor justified a sponsor's requirement by (falsely) *blaming the FDA*. Perhaps someone thought some practice seemed like it *should be* a regulation and just passed it on. Perhaps someone just wanted to *play it safe*. However it happened, the clinical research enterprise is now littered with presumed regulations that might be good ideas but are not actual governmental requirements.

This article discusses some regulatory requirements that may or may not be myths — test your own knowledge. These "requirements" are far from an exhaustive list, nor are they the Top Ten (or 14), but they are a start on applying Mark Twain's observation on what we know that just ain't so.

FDA Regulations

The FDA requires that everyone involved in a research study needs to be listed on Form 1572.

FALSE. You must list principal investigators and clinical research coordinators, since they play a significant role in the study. List sub-investigators as well, since the FDA will assume that they, too, play a significant role. However, nurses, medical residents, fellows, lab technicians, data entry clerks? Probably not. The only people who have to be listed are those that make a "direct and significant contribution to the data." (21 CFR 312.53(c)(1)(viii))

FDA Form 1572 must be submitted as a double-sided copy.

FALSE. You can submit 1572 forms either as a double-sided sheet or as two single-sided sheets, stapled together so there is no question about what form the investigator signed.

FDA Guidance must be followed.

FALSE. Regulations are requirements. Guidances are suggestions. If you follow a guidance, you are following the FDA's interpretation, so you will probably avoid regulatory issues. However, it might be better to "do the right thing," especially if study participant safety is involved.

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The FDA requires that consent forms be written at an eighth-grade reading level.

FALSE. No FDA (or OHRP) regulation requires a specific reading level. The regulatory requirement is that, during the informed consent process, "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, also 45 CFR 46.116) Some consent forms are so obscure that only the scientists or lawyers that wrote them can understand their meaning. On the other hand, some patients with chronic diseases become so expert in their condition that they know more about it than the study nurse. Writing at the eighth-grade (or lower) level is a reasonable standard, but still does not ensure understanding, given the high rate of illiteracy and the challenge of reading a 20- or 30-page document. Therefore, the informed consent process must always include substantial verbal discussion. Remember, informed consent is a process, not just a document.

The FDA approves protocols.

PARTIALLY TRUE. The FDA must approve (actually, not disapprove) a protocol, but its approval is not enough. IRB approval is also required, without exception. Even if IRBs at Sites A through Y have approved a protocol, Site Z's IRB has every right to decline to approve the study at its institution.

Study drug must be stored in a locked cabinet in a locked room.

MOSTLY FALSE. The regulations discuss only controlled substances, not all test articles: "If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution." (21 CFR 312.69) You can easily imagine how this got expanded to cover *everything*.

Protocol/IRB Review Issues

IRBs can approve a study based on societal or scientific benefits.

TRUE. The regulations state: "Risks to subjects [must be] reasonable in relation to anticipated benefits, if any, to subjects, and *the importance of the knowledge that may reasonably be expected to result*. [italics added for emphasis]" (45 CFR 46.111(a)(2) and 21 CFR 56.111.(a)(2))

The same regulations also state: "The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility." In other words, immediate risks to study participants should be considered, but not long-range risks due to application of the study's findings.

Sponsor-directed amendments or modifications to a protocol need IRB review and approval.

MOSTLY TRUE. Sponsors are entitled to their opinions, but IRBs make the decisions that matter. The regulations state: "An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations." (45 CFR 46.109(a) and 21 CFR 56.109(a)) However, fixing typos or changing administrative information probably does not constitute a change in the "research activities." Although this regulation does not literally say that IRB approval is required, we

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presume that that is what the authors meant to say. It would take a brave investigator to argue otherwise.

A research site can enroll a subject who does not quite meet eligibility criteria if the sponsor provides a waiver.

FALSE. Enrolling a study participant who does not mean the eligibility criteria is a protocol deviation, full stop. The IRB approves protocol as submitted, with no fuzzy edges. FDA regulations state: "The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will *not make any changes in the research without IRB approval* [italics added for emphasis], except where necessary to eliminate apparent immediate hazards to human subjects." (21 CFR 312.66) However, if the sponsor does not object, the IRB is unlikely to have an ethical issue if the deviation is trivial. Nevertheless, it's up to the IRB to decide what constitutes triviality.

Consent forms must specify compensation amounts for study-related injuries.

FALSE. The regulations state: "When appropriate, one or more of the following elements of information shall also be provided to each subject:… Any additional costs to the subject that may result from participation in the research." (CFR 50.25 (b)) However, in most cases, it's simply not practical to specify exact dollar amounts.

Document Management Issues

Several document concepts have moved from practices and procedures into the land of regulatory myth. The most common among these are:

Study participants must initial and date every page of the informed consent form.

FALSE. There is no regulation to this effect. An IRB (or sponsor) might require this as a specified local practice, but there is no regulatory requirement.

The investigator must sign the informed consent form.

FALSE. There is no regulation to this effect.

Investigator CVs must be signed and dated, and then updated every two years.

FALSE. There is no regulation to this effect.

Conclusion

It's impossible to know how much time is wasted complying with the regulatory myths listed above and countless others. So, what can we do about it? To start with, periodically reread the main regulations. Second, maintain a healthy level of skepticism when someone says something is an FDA requirement. Ask to see the regulation. When in doubt, look it up.

When the IRB says, "no, you can't do that" (but you're not sure why), ask them to explain *in writing* the regulatory and local institutional basis for the disapproval. The regulations state: "An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it

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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." (21 CFR 56.109(e))

Thirdly, try not to invent or propagate new myths. When you ask someone to do something, or write a standard operating procedure, don't say it's an FDA requirement unless it really is.

And, lastly, help identify other regulatory myths. Please send in your examples for the next edition of this article. Or, if one of the rules categorized above as a myth is not actually a myth, please explain.

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