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Yet More Regulatory Myths

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Researchers and IRB members make their best efforts to comply with the regulations, but sometimes what they are doing is not required, or might even be contrary to the regulations. These mistaken beliefs can spread through an organization and beyond. The regulations and guidance documents are readily accessible, so why do these actions and beliefs (hereafter myths) persist?

The answer might lie in the nature of storytelling. When a story is told, it can change. The mind has a tendency to remember the major points and to forget the minor details. As a result, important elements can get lost or distorted. In addition, people have a tendency to take things apart and put them back together in ways that make them easier to understand.[1] The complexity — and often ambiguity — of clinical research regulations invite interpretive drift, especially when a regulation or guidance is not easily at hand and the listener respects the expertise of the speaker.

Common errors include misinterpreting or misapplying the regulations, confusing regulatory requirements with institutional policies, and inappropriately extrapolating current or former regulations.

For example, *everyone* knows that any planned protocol deviation for a study is considered a change in research that needs prior IRB approval. However, *for non-federally funded device studies not being conducted under an FWA*, the regulations require the reporting of a planned protocol deviation *only* if it might adversely affect the rights, safety or welfare of subjects or the integrity of the research data. (See: See 21 CFR 56.108(a)(4) and 21 CFR 812.35.)

Regardless of their origins, which of the following "regulatory requirements" are actually requirements, and which are just myths?

An IRB can accept an investigator's determination that an investigational device study qualifies as a non-significant risk device without making its own analysis.

FALSE. Responsibility for determining whether a device study qualifies as a non-significant risk (NSR) device study lies with the sponsor and the IRB. The IRB can agree with the sponsor's or investigator's rationale that a device qualifies as a non-significant risk device, but the IRB must evaluate the use of the device in the study and make its own determination. FDA has the final authority to determine whether a device is NSR.

A retrospective chart review study approved under CFR 45 Part 46.101(b)(4) can include information collected after the exemption was granted if the information is collected under standard of care.

FALSE. All of the information to be collected has to be in existence when the exemption is granted. Information collected after an exemption is granted is considered "prospective collection" and thus does not meet the b(4) exemption, even if the information is being collected for non-research purposes.

The only criterion necessary to waive consent is that the research is minimal risk.

FALSE. The research must meet all requirements of 45 CFR 46.116(d):

1) Minimal risk
2) Will not adversely affect the rights and welfare of the subject
3) Impracticable to do the research without a waiver of consent
4) When applicable, the subject is provided additional information about the study.

The IRB chair is the only IRB member allowed to perform expedited review.

FALSE. 21 CFR 56.110 and 45 CFR 46.110 place no such requirement, so any experienced IRB member who is designated by the IRB Chair to be an expedited reviewer can perform expedited review.

A study that uses coded biosamples from an outside source is exempt from IRB review because the investigator does not have the codes to identify the donors.

FALSE. To be exempt, the subjects cannot be identifiable, either directly or indirectly. In this case, the codes provide links back to the individuals who provided the samples. It does not matter that the investigator does not know their names. The 45 CFR 46.101(b)(4) exemption does not apply because the samples are indirectly identifiable.

Adverse events that are reportable to the FDA also must be reported to the IRB.

FALSE. Only unanticipated problems must be reported to the IRB. In 2009, the FDA published guidance explaining what needs to be reported to the IRB. Submitting adverse events (AEs) to the IRB does not give the IRB enough information to know whether they constitute an unanticipated problem. Generally, the IRB does not have all of the information regarding how many subjects have been enrolled in the study, how many have had this AE, or whether the frequency of the AE is expected. The FDA guidance requires the reporting party (usually the sponsor) to analyze the AEs to determine whether they constitute Unanticipated Problems that Represent an Increase Risk to Subjects or Others. If so, the unanticipated problem must be reported to the FDA. The guidance is available at: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126572.pdf.

IRB minutes must document how each member votes on study approvals.

FALSE. There is no requirement to record votes by individual members. 21 CFR 56.115 and 45 CFR 46.115 both state:

> An institution, or, when appropriate, an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:
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> > (2) Minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions, including the number of members voting for, against and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

Eligibility exceptions, if minor, for clinical trials do not require IRB review when the sponsor has granted approval.

FALSE. 21 CFR 56.108 states:

> In order to fulfill the requirements of these regulations, each IRB shall:
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> Follow written procedures: (4) 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 except where necessary to eliminate apparent immediate hazards to the human subjects.

Any change in eligibility requirements, even if minor and for only one subject, are planned protocol deviations that need prior IRB review.

For a device study, a change in the eligibility criteria, even for one subject, must be assessed to determine whether it would affect the rights, welfare and safety of the subject and, if so, would need prior IRB review as well. *See* 21 CFR 812.35.

An investigator cannot determine that his or her study is exempt from IRB Review.

FALSE, mostly. The regulations do not specify who can determine that a study is exempt from IRB review. However, guidance from OHRP states that, due to the inherent conflict, the investigator should not make a determination that his or her study is exempt from IRB review. This guidance is available at: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/exempt-research-determination/index.html.

The presence of an IRB member who is recused due to a conflict of interest still counts towards quorum.

FALSE. 21 CFR 56.107 states:

> No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

As a result, if there is only one non-scientist present and the non-scientist has the conflict of interest, the meeting has lost quorum.

Interviews and focus groups are always exempt from IRB Review.

FALSE. Depending on the topic, an interview or focus group could carry greater than minimal risk. If disclosure of the subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation, the study is not exempt. *See* 45 CFR 46.101(b)(2).

A case study on an individual patient, for the express purpose of publishing an article in a medical journal, requires IRB review.

FALSE. Publication, or the intent to publish, does not make the information generalizable and therefore does not create a requirement for IRB review. In this case, the information is collected as part of standard clinical care and does not constitute research. Publishing the case study does not change its character to research. However, an institution might create a threshold for the number of case studies it would consider to be research, e.g., that

developing more than three case studies creates generalizable knowledge and is therefore subject to IRB review.

A disclosure of private subject data is a HIPAA violation that must be reported to the IRB.

DEPENDS. The investigator or institution must analyze the situation to determine if it constitutes an Unanticipated Problem Involving Risks to Subjects or Others. If so, it must be reported to the IRB.

If a subject withdraws from a study, he or she may require that his or her confidential study data be removed from the study records.

FALSE. FDA's "Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials" states:

> Data collected on study subjects up to the time of withdrawal must remain in the trial database in order for the study to be scientifically valid. If a subject withdraws from a study, removal of already collected data would undermine the scientific, and therefore the ethical, integrity of the research. Such removal of data could also put enrolled subjects, future subjects, and eventual users of marketed products at an unreasonable risk. Finally, removal of data would fundamentally compromise FDA's ability to perform its mission, to protect public health and safety by ensuring the safety and effectiveness of regulated products.
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> The guidance can be found at:
> http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf.

The IRB must approve meeting minutes.

FALSE. OHRP's and FDA's joint draft guidance, "Minutes of Institutional Review Board (IRB) Meetings: Guidance for Institutions and IRBs," includes no such requirement:

> We recommend that institutions and IRBs decide who is responsible for preparing and maintaining minutes at their institutions and outline the process in the IRB's written procedures. If the institution and IRB have a process for review and either acceptance or approval of minutes, this process should be covered in the IRB's written procedures.

The guidance is available at
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM470154.pdf.

The IRB chair must sign action letters (e.g., notifications of approval or disapproval).

FALSE. DHHS and FDA regulations do not require the IRB chair to sign written notifications. When the regulations are silent, IRBs and institutions may develop their own procedures and practices, provided applicable regulatory requirements are met.

For more information, see the FDA FAQs at:
http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm#IRBRecords.

IRB review at a convened meeting is required for a study that involves quality-of-life questionnaires, medical record reviews, and annual physical

exams to track the long-term safety of subjects who receive an investigational medication conducted under an IND.

TRUE. Since the study involves an investigational drug, it will be conducted under an IND. The OHRP and FDA expedited review criteria state:

> Clinical studies of drugs and medical devices only when condition (a) or (b) is met:
>
> (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
>
> (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

The expedited review criteria can be found at: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html.

Children must assent to participate in research.

FALSE. 21 CFR 50.55 and 45 CFR 46.408 state that assent of minor subjects is not necessary in a clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

The withdrawal of life support for a terminal oncology subject and subsequent death (not related to study participation) must be reported to the IRB.

DEPENDS. If the removal of life support is not related to the study, the subject's death does not need to be reported to the IRB. Also, since terminal subjects are expected to die from their underlying disease, the death of a subject choosing to withdraw life support is not an unanticipated problem that must be reported to the IRB.

The regulations require a PI document, by signature, that all inclusion/exclusion criteria have been met for enrolled subjects.

FALSE. The requirements for records retention for "case histories" for research involving drugs and devices are similar: neither require that a PI document by signature that all inclusion/exclusion criteria have been met. However, the documentation maintained should be sufficient to allow an independent assessment that the eligibility criteria were met. See CFR 312.62 and 21 CFR 812.140.

The IRB is responsible for notifying the PI prior to any lapse of approval.

FALSE. The IRB's can notify the PI as a courtesy, but the FDA Guidance, "IRB Continuing Review after Clinical Investigation Approval" (2012), does not require such notification:

> Investigators are responsible for ensuring that studies they conduct comply with applicable regulatory requirements. To ensure that the reviewing IRB can carry out its review prior to the expiration date of the current IRB approval, investigators should follow the IRB's policies and procedures for continuing IRB review of research (procedures required by 21 CFR 56.108(a)(1)), in particular by submitting materials and information required by the IRB. FDA encourages IRBs to make investigators aware of the IRB's procedures, for example, by enclosing a copy in correspondence informing the investigator of the IRB's decisions, or posting the information on a website.

See also 21 CFR 312.53(c)(1)(vii), 312.60, 312.66, 812.36(c)(viii), 812.100, 812.110(b), 812.40, and 812.43(c)(4)(i).

Disclaimer

Regulations can change and the agencies are constantly issuing guidance that clarifies or alters their interpretation, so the next time you think you know the regulations, you might discover a myth has become a requirement or a requirement a myth.

Reference

1. James Bonnet, How the Great Myths and Legends Were Created. The Writers Store. www.writersstore.com/how-the-great-myths-and-legends-were-created. (Accessed 06-05-2016)

Previous Articles about Regulatory Myths

"Regulatory Myths in Clinical Research," Brian A. Gladue, Journal of Clinical Research Best Practices, September 2014

"More Regulatory Myths in Clinical Research," Brian A. Gladue, Journal of Clinical Research Best Practices, May 2015

"Even More Regulatory Myths in Clinical Research," Parker Nolen, Journal of Clinical Research Best Practices, January 2016

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