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Still More Regulatory Myths

By Rebecca Rogers

Myths are entrenched beliefs, such as human subject research practices that are widely considered regulatory requirements, but, in fact, are not required. U.S. law and guidance regulates human subject research. In addition, international guidelines, such as ICH E6, state regulations, sponsor-specific requirements, and site-specific policies and procedures also govern research conduct. When conducting clinical research, it can be helpful to know the source of a specific requirement, or whether it exists at all.

The following myths are based on U.S. federal regulations and guidance. Your state, institution or study sponsor might have rules that exceed or differ from these requirements.

A single form can include both the informed consent and the HIPAA authorization.

TRUE most of the time. An authorization for the use or disclosure of protected health information for research may be combined with consent to participate in the research, or with any other legal permission related to the research study. However, the Privacy Rule requires a covered entity to obtain "individual" (i.e., separate) authorization prior to a disclosure of psychotherapy notes. Most organizations use a separate authorization form for this purpose. (See: https://www.hhs.gov/hipaa/for-professionals/faq/546/does-hippa-permit-a-covered-entity-to-disclose-psychotherapy-notes/index.html)

eConsent systems do not need to be approved by the IRB; provided a paper informed consent form is approved.

FALSE. An IRB must review the eConsent system. The IRB has to ensure there is an adequate informed consent process that protects the rights and welfare of subjects participating in HHS-regulated research and FDA-regulated clinical investigations. See 45 CFR 46.109(b) and 21 CFR 56.109(b) and 56.111(a)(4). The IRB needs to review the platform for usability and ease of use, all hyperlinks, and the consent wording. (See: FDA guidance "Use of Electronic Informed Consent")
http://www.fda.gov/downloads/drugs/guidances/ucm436811.pdf

The Federal Regulations require the consent document to be translated prior to consenting of a non-English-speaking subject.

TRUE. The full consent form can be translated and used. Or, if using the short form consenting process, a short-form consent document can be translated and used in conjunction with the full English-language consent document. The subject, a witness, and the person obtaining consent can sign the short-form consent document. In either case, an IRB must approve the translated consent document. See OHRP "Informed Consent of Subjects Who Do Not Speak English" at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/obtaining-and-documenting-infomed-consent-non-english-speakers/

Federal Regulations prohibit a family member from being a witness.

FALSE. Federal regulations do not include this prohibition. ICH E6 (1.26) says an impartial witness is a "person independent of the trial, who cannot be unfairly influenced by people involved in the trial." (ICH E6 GCP 1.26)

IND Safety reports must be sent to the IRB.

FALSE. No federal regulations, ICH guidelines, or OHRP guidances stipulate that IND safety letters must be sent to an IRB. The site must report unanticipated problems involving risks to subjects or others to the IRB; but most IND safety reports do not meet the definition of an unanticipated problem.

When working with an external IRB, I can just inform the IRB and do not need to separately inform my institution of unanticipated problems involving risks to subjects or others, serious non-compliance or continuing non-compliance, or suspension or termination of IRB approval.

TRUE, provided there are written procedures for the IRB to promptly inform the "appropriate institutional officials and the department or agency head." (45 CFR 46.103 (b)(5))

All adverse events that are reportable to the FDA are required by regulation to be reported to the IRB.

FALSE. Only AEs that meet the definition of an unanticipated problem or serious or continuing noncompliance need to be reported to the IRB. See: "Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs Improving Human Subject Protection" at http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126572.pdf. An AE-reporting decision tree can be found at http://www.hhs.gov/ohrp/policy/advevntguid.html#AB

The principal investigator must determine whether an event qualifies as an unanticipated problems involving risks to subject or others, serious non-compliance, or continuing non-compliance.

FALSE. 45 CFR 46.103(b)(5) does not specify who makes the determination.

An IRB meeting cannot vote to approve a study unless a community member is present.

FALSE. FDA's "Institutional Review Boards Frequently Asked Questions – Information Sheet" says "Although 21 CFR 56.108(c) does not specifically require the presence of a member not otherwise affiliated with the institution [i.e., a "community member"] to constitute a quorum, FDA considers the presence of such members an important element of the IRB's diversity. Therefore, frequent absence of all non-affiliated members is not acceptable to FDA."

An investigator's study documents and records must be stored in a location behind two locks.

FALSE. The FDA says only that it "expects that reasonable steps would be taken to maintain control of the study records, the privacy and confidentiality of study subjects, and the confidentiality, completeness and accuracy of study records." (http://www.firstclinical.com/fda-gcp)

Our site does not use digital signatures, so 21 CFR Part 11 does not apply to us.

FALSE. 21 CFR Part 11 has *two* parts: Subpart B – Electronic Records *and* Subpart C – Electronic Signatures. Part 11 applies to any FDA predicate rule requiring a record, such as

21 CFR 312, 812, 50, 56 and 1271, including documents in electronic regulatory binders, IRB administration systems, research records, and all "eTools." See the FDA draft guidance dated June, 2017, "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under Part 11 – Questions and Answers; Draft Guidance for Industry," at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM563785.pdf

A Non-significant Risk (NSR) device (once so determined by an IRB) will always be NSR.

FALSE. The IRB's risk determination takes into account not only the properties of the device, but also how it is to be used in a particular study. If either changes, then the IRB has to re-assess the risk. Protocol modifications, including changes in the use of the device, study population, or software, might change the risk level of the device.

NIH RAC review is no longer required for human gene transfer studies.

FALSE. An IRB or IBC *may* determine in certain situations that a NIH RAC review is required for a human gene transfer study.

RAC Review Procedures Revised Under the NIH Guidelines effective April 27, 2016: …. *(RAC) review of individual human gene transfer trials should be limited to cases in which an oversight body (such as an Institutional Biosafety Committee or an Institutional Review Board) determines that a protocol would significantly benefit from RAC review.*

As before, all human gene transfer protocols subject to the *NIH Guidelines* will continue to be registered with the NIH and be reviewed and approved by institutional oversight bodies, such as the IBCs and IRBs. Documentation submitted to the NIH shall also include written assessments originating from all oversight bodies involved in the review at an initial site(s) as to whether RAC review is warranted.

From:
https://www.gtrp.org/Public/Documents/Human%20Gene%20Transfer_FAQ%20sheet.pdf

Conclusion

Federal human subject research regulations are often misstated and interpreted in different ways. Even determining WHICH federal level regulations apply to a specific research project is challenging. Regulations and federal guidance documents are being published, revised, and updated frequently. While human subject research project compliance with ALL applicable FEDERAL regulations is required, this article has also stressed that there may be MANY "layers" of non-regulatory requirements to be met when conducting human subject research. Researchers and their teams need a thorough awareness of applicable federal regulations, as well other regulatory expectations, prior to study start up.

Disclaimer

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

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

"Yet More Regulatory Myths in Clinical Research," R. Bert Wilkins, Journal of Clinical Research Best Practices, August 2016

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