COMPLIANCE LETTERS

January 15, 2014
IRB Forum
Office of Human Research
The George Washington University
Overview

- Determination Letters (OHRP)
- Warning Letters (FDA)
- Review of letters
DETERMINATION LETTERS

Office of Human Research Protections (OHRP)
Determination Letters

- Office of Human Research Protections (OHRP) Division of Compliance Oversight (DCO) evaluates written allegations of noncompliance with Federal Regulations (45 CFR 46).
- DCO also conducts a program of not-for-cause surveillance evaluations of institutions, and receives, reviews, and responds to incident reports from Assured institutions (those holding a FederalWide Assurance).
Determination Letters

http://www.hhs.gov/ohrp/compliance/evaluation/index.html

• (1) OHRP determines whether the office has jurisdiction to evaluate the allegations or indications of noncompliance at the relevant institution(s).
• (2) OHRP notifies any complainant
• (3) OHRP sends officials at the institution(s) engaged in the research an initial inquiry letter informing them that our office is evaluating human subjects research protections at their institution(s).
• (4) OHRP sends copies of the initial inquiry letter to the principal investigator(s) of the specific research project(s) at issue.
• (5) OHRP evaluates the documentation submitted by the institution in response to OHRP's initial inquiry letter to determine whether additional information is needed for OHRP to determine whether there is evidence of noncompliance with the HHS regulations.
Determination Letters

http://www.hhs.gov/ohrp/compliance/evaluation/index.html

• (6) OHRP engages external expert consultants to assist as needed.
• (7) If OHRP has specific additional questions or concerns that can be addressed by the institution in writing, OHRP will present these questions and concerns in additional written correspondence to the institution.
• (8) Based on the institution's responses and any relevant information received from the complainant or other sources, OHRP issues one or more letters to the institution containing OHRP's determinations.
• (9) OHRP informs the complainant in writing of OHRP's determinations and any corrective actions taken by the institution upon completion of the evaluation.
• (10) An institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation.
WARNING LETTERS

Food and Drug Administration (FDA)
Warning Letters

• Most FDA inspections are routine for studies that are pending New Drug Application review.
• However, directed, or for cause inspections can be initiated by suspicion of false or fraudulent data. This is data that may appear unrealistic, or if the sponsor alerts the FDA of serious problems.
• Warning Letters are issued only for violations of regulatory significance.
• Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected.
Warning Letters

- A Warning Letter is the agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the Act).
- A Warning Letter is informal and advisory. It communicates the agency's position on a matter, but it does not commit FDA to taking enforcement action.
- For these reasons, FDA does not consider Warning Letters to be final agency action.
In determining whether to issue a Warning Letter, district directors and center or other officials with authority to issue should consider whether:

- Evidence shows that a firm, product, and/or individual is in violation of the law or regulations and that failure to achieve adequate and prompt correction may result in agency consideration of an enforcement action;
- The violation(s) are determined to be of regulatory significance, and the issuance of a Warning Letter is appropriate and consistent with agency policy, as described in Compliance Policy Guides or elsewhere; and,
- There is a reasonable expectation that the responsible firm and persons will take prompt corrective action.
CASE STUDIES

- Waiver of Consent (VCU)
- Language Barrier (Dignity Health)
- Exempt Research (University of Iowa)
- Consent Issues (University of Minnesota and University of South Florida)
- FDA Violations (Dr. Velhamos)
Waiver of Consent (VCU)
45 CFR 46.116(d) and 45 CFR 46.117(c)

• Citations generated by submission of a progress report from VCU.
• It was noted an investigator requested Waiver of Consent for enrollment and recruitment. This was not allowable under the federal regulations for this study.
• Waiver of Documentation: In some cases, an IRB may waive the requirement for documentation of informed consent.
• Waiver of consent: An IRB may waive or alter the requirement of informed consent provided that the IRB finds and documents that all of the following four conditions are met:
  • the research involves no more than minimal risk to the subjects;
  • the waiver or alteration will not adversely affect the rights and welfare of the subjects;
  • the research could not practicably be carried out without the waiver or alteration; and
  • whenever appropriate, the subjects will be provided with additional pertinent information after participation.

• [Link](http://www.hhs.gov/ohrp/detrm_letrs_sep00d.pdf)
Language Barrier (Dignity Health)

• Per an allegation of noncompliance, an inspection was conducted by OHRP for two studies.
• Both studies involve the use of non-English speaking individuals.
• Letter states it is alleged that consent was not conducted in a language understandable to the subject or the subject’s legally authorized representative, per 45 CFR 46.116.
• The issue was resolved as 1) the PI closed the study and 2) a member of the research team was fluent in the languages in which subjects were being enrolled.

• [http://www.hhs.gov/ohrp/detrm_letrs/YR13/jul13d.pdf](http://www.hhs.gov/ohrp/detrm_letrs/YR13/jul13d.pdf)
Exempt Research (Univ Iowa)
45CFR46.101(b)

• During a routine inspection at University of Iowa, this study was noted to be erroneously categorized as Exempt.
• Exempt does not mean it is exempt from submission for review. It means it is Exempt from federal regulations.
• There are six categories of Exempt research. A study must meet one of those six categories in order to be Exempt.
  • Research in educational settings
  • Educational testing, surveys, interviews or observation of public behavior
  • Research involving elected public officials- Extension of Category 2 without the same level of oversight for the subject’s privacy
  • Research involving existing data (retrospective only)
  • Demonstration projects
  • Taste of food quality evaluation

• http://www.hhs.gov/ohrp/detrm_letrs/YR12/sept12a.pdf
Consent Issues (Univ Minn and Univ South FL)

• In an allegation of noncompliance, an investigation was conducted for a collaborative study involving University of Minnesota (UM) and University of South Florida (USF), in which USF served as data coordinating center and did not conduct any subject related research activities.

• One allegation was failure to disclose study risks. It was noted that indeed, UM did not include any foreseeable study related risks and discomforts.

• This is a violation of 45 CFR 46.116(a)(2).

• http://www.hhs.gov/ohrp/detrn_letrs/YR12/nov12a.pdf
FDA Violations (Dr. Velhamos)

21CFR312

• Failure to obtain the informed consent of each human subject...

• …and Failure to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations, and to protect the rights, safety, and welfare of subjects under your care.

• It is important to follow the research plan as submitted to the IRB and other regulatory agencies.

• http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm377810.htm

• http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm380581.htm
Questions??

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OHRP Determination Letters:
http://www.hhs.gov/ohrp/compliance/letters/index.html

FDA Warning Letters:
http://www.fda.gov/iceci/enforcementactions/warningletters/default.htm