Celebrating our 34th year published every month - Now emailed!

Human Research Report

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

Volume 34, No. 1 ISSN 0885-0615 January, 2019

How to Interpret New "Exemptions" From Regulations and IRB Review - Pt. 1

The Secretary's Advisory Committee on Human Research Protections (SACHRP) has released another new set of five different recommendations for IRBs, researchers, and others on how to implement the new "2018 Requirements" in the revised Common These new major and complicated requirements, numbering in the dozens, become effective this month, on January 19.

In addition to SACHRP's November 13 summary cover letter to Alex Azar, Secretary of the Department of Health and Human Services, SACHRP included five "Attachments." The Attachments contain SACHRP's detailed recommendations, titled as follows: "Attachment A - Response Office Inspector General Report, July 7, 2017," "Attachment B - Interpretation Revised Common Rule Exemptions," "Attachment C - New 'Key Information' Informed Consent Requirements," "Attachment D - Parental Permission in Research Involving Children," and "Attachment E - Transition Provisions and Informed Consent Requirements."

We will present key highlights of the other Attachments in future HRRs.

Exemptions Have Crucial Details

We begin our coverage of these vital recommendations (especially for IRBs and researchers) with highlights of "Attachment B" on exemptions from the Common Rule (including exemption from IRB review).

"Background

The pre-2018 regulations at 45 CFR 46.101 identify six categories of research that are exempt from the requirements of the policy. These exemptions are described at §46.101(b)(1)-(6). In the 2018 revision to 45 CFR 46, the exemptions have been moved to §46.104(d) and expanded into eight categories" ("Attachment B - Interpretation Revised Common Rule Exemptions, November 13, 2018, p. 1 of 8; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-november-13-2018/index.html).

Although categories one and two have retained their original areas of focus, there are modifications to the language that will require the individual making a determination of exemption to consider new factors that may impact the applicability of the exemptions to proposed activities.

SACHRP has been asked to provide input on

NOTE #1: Quoted materials in this newsletter appear exactly as originally published in source documents, including any misspellings, grammatical errors, missing words, etc. However, we will on occasion insert words of our choice in brackets [ ] to make the material easier to read, or edit paragraph formatting.

NOTE #2: Emphases are added to articles by HRR by underlining or adding ***bold/italics*** to selected text, unless stated otherwise.

NOTE #3: Articles to be continued in subsequent issues are marked at the end with **{TBC}** ("To Be Continued").

Also In This Issue

Published monthly by The Deem Corporation, P.O. Box 451117, Omaha, NE 68145. Editor and Publisher: Dennis M. Maloney, Ph.D.

the interpretation of the revised language as well as on longstanding areas of debate from the original language of the exemptions.

Changes to Exempt Category 1

Exemption 1 with emphasis on differences between pre-2018 rule and 2018 rule:

(1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods**"** (p. 1 of 8).

What Does "Education Setting" Really Mean?

"Within the regulated community there is an assumption that the original intent of the category 1 exemption may have been to cover educational settings under the jurisdiction of the US Department of Education (ED), which would typically be afforded the basic privacy protections for educational records that are provided by the Family Educational Rights and Privacy Act of 1974 (FERPA).

However, there is no existing guidance that limits the use of the category in this way, and contemporary use of exemption 1 as it appears in the pre-2018 Common Rule has expanded to include anything that could be described as an established or commonly accepted educational setting.

In addition to traditional K through 12 and post-secondary settings, use of the exemption has been applied to diverse settings, including professional development seminars, Boy Scout meetings, religious education, drivers education, and educational experiences utilizing various types of training simulators.

The structure of the exemption categories in the 2018 Common Rule suggests that educational settings under the jurisdiction of ED remains the intended scope of the regulation, regardless of how it has come to be used in practice. Specifically, nearly all other exemptions that deal with private information now have explicit measures to protect such information.

Exemption 2, which is largely methodology based, now requires that the information be unidentifiable, or that disclosure does not create risk, or that a limited IRB review ensure confidentiality protections are adequate.

The same protections are provided for exemption 3. Exemption 4 provides similar protections by substituting HIPAA or Privacy Act provisions for limited IRB review. Exemptions 7 and 8 rely on broad consent and consequently voluntary and informed participation.

Exemption 5 is the only other exemption that will routinely allow access to private information and that provides no implicit or explicit privacy protections. However, exemption 5 is largely a jurisdictional exemption to allow Federal departments and agencies the latitude to evaluate and improve their programs; it contains the requirement that notice be provided of any such exempt research before it is started.

Absent the assumption of FERPA jurisdiction, exemption 1 is the only exemption that contains neither privacy protections nor a requirement for notice or voluntary participation.

Exempt Category 1 Questions for SACHRP:

Q: What are considered '… established or commonly accepted educational settings' …?

[A:] The consistent interpretation among IRBs is that commonly accepted educational settings can be almost anywhere as long as the setting is one where specific educational offerings normally take place or a setting where one would go in order to have an educational experience.

IRBs do not appear to consider the source of funding for proposed research or the applicability of other protections, e.g. FERPA.

Examples of settings identified by SACHRP include:

- K-12 schools and college classrooms, afterschool programs, preschools, vocational schools, and alternative education programs
- professional development seminar for school district personnel
- soccer practice field
- Scouts meeting
- Medical school
- Religious education settings
- Training simulators (e.g., medical simulators, flight simulators, etc.)**"** (supra at p. 2-3).

{TBC} ©

IRBs Have New Informed Consent Alterations/Waivers Possible - Pt. 2

We continue here with a significant proposal by FDA on informed consent regulations and allowing IRBs to alter informed consent elements or, in certain circumstances, even to waive its need altogether. Obviously, such a change would permit IRBs, researchers, and FDA staff to save much needed time, and to potentially make it easier to recruit and enroll otherwise hesitant research subjects who might find such documents daunting in some cases.

The recent FDA announcement was made on November 15, 2018, in the FEDERAL REGISTER. FDA set their comment deadline for this proposal for January 14, 2019, as we noted in last month's initial HRR article on this development. However, on December 20, 2018, FDA issued an extension of that comment deadline to February 13 (83 Fed. Reg. 65322). The extension was due to one request for said extension.

Below we resume our coverage where we left off in last month's HRR, as follows.

Traditional Authority to Alter Or Even Waive Informed Consent

"The Common Rule standard has permitted an IRB to waive the requirements to obtain informed consent, or to allow changes to, or omission of, some or all elements of informed consent if the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver or alteration; and

(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116(d); 56 FR 28001 at 28017).[2]

[FN #2: References to the Common Rule in this document are to the 1991 version of the Common Rule, unless otherwise noted. A final rule that revised the 1991 version of the Common Rule adopted an effective and general compliance date of January 19, 2018 (82 FR 7149, January 19, 2017).

On January 22, 2018, an interim final rule was published that delayed the effective and general compliance date of the revisions until July 19, 2018 (83 FR 2885).

On June 19, 2018, a final rule was published that further delays the general compliance date until January 21, 2019, while allowing the use of three burden-reducing provisions for certain research during the delay period (83 FR 28497).

The revised version of the Common Rule, including amendments made by the January 22, 2018 interim final rule and the June 19, 2018 final rule, is referred to in this document as the 'revised Common Rule.']

FDA amended its regulations in parts 50 and 56 to conform them to the Common Rule in 1991 (56 FR 28001 at 28025) but diverged from the Common Rule's provision for waiver or alteration of informed consent for minimal risk research at 45 CFR 46.116(d).

In explaining the reason for this departure, FDA cited sections 505(i) and 520(g)(3)(D) of the FD&C Act and stated that the FD&C Act 'requires informed consent to be obtained from all subjects except in very limited circumstances' and that the Agency did 'not have the authority under the act to waive this requirement' (53 FR 45671 at 45679, November 10, 1988)**"** (83 Fed. Reg. 57378-57386 at pp. 57380, Nov. 15, 2018).

"Minimal Risk" Is Key Factor For FDA-Regulated Products

"The Common Rule provision recognizes that there may be proposed research that cannot practicably be conducted without a waiver or alteration of informed consent, but the research would contribute valuable medical or scientific knowledge and would present no more than minimal risk to subjects. FDA believes this is also true for some minimal risk FDA-regulated clinical investigations.

On March 13, 2014, the Secretary's Advisory Committee on Human Research Protections (SACHRP) considered whether the Common Rule standard for waiver of informed consent for minimal risk research would be appropriate and helpful for FDA-regulated clinical investigations. SACHRP recommended to the Secretary of HHS that FDA adopt the provisions for waiver of informed consent that existed under the Common Rule at that time at 45 CFR 46.116(d).

On October 26, 2016, SACHRP reiterated that recommendation to the Secretary.[4]

[FN #4: SACHRP's recommendations are available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2014-july-3-letter-attachment-c/index.html; and at https://www.hhs.gov/ohrp/sachrpcommittee/recommendations/attachment-b-november-2-2016-letter/index.html.] (supra at p. 57381). **{TBC}** ©

New Procedures for IRBs in "Master Protocol" Studies - Pt. 2

As we first presented in last month's HRR (see pp. 1-2), human subject studies using "master protocols" pose significant challenges for IRBs and researchers who use such experimental designs. Those challenges include research subject safety issues, as well as subject selection, enrollment, and retention issues that are relevant for IRB reviews of applicable protocols.

The new FDA guidance on these special types of human subject studies points out that:

> **"**... a master protocol is defined as a protocol designed with multiple substudies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure**"** ("Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics," September, 2018, p. 3 of 12; on the Web at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621817.pdf).

Human Subject Safety Is a Prime Concern In "Master Protocol" Studies

> **"**In general, FDA strongly recommends that the sponsor [including a researcher-sponsor] establish the RP2D [recommended Phase 2 dosage] for the investigational drug(s) before evaluation using a master protocol.
>
> Individual drug substudies under the master protocol can incorporate an initial dose-finding phase, for example, in pediatric patients when sufficient adult data are available to inform a starting dose and the investigational drug provides the prospect of direct clinical benefit to pediatric patients.[7]
>
> [FN #7: 21 CFR 50 subpart D.]
>
> A master protocol may be used to conduct the trial(s) for exploratory purposes or to support a marketing application and can be structured to evaluate, in parallel, different drugs compared to their respective controls or to a single common control.
>
> The sponsor can design the master protocol with a fixed or adaptive design[8] with the intent to modify the protocol to incorporate or terminate individual substudies within the master protocol.
>
> [FN #8: See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, the guidance will represent FDA's current thinking on this topic.]**"** (ibid).

As we can see in the next section of this new guidance, the issue of human research subject safety is a prime concern in this type of research. Obviously, this is a major concern of IRBs as well.

> **"**The potential advantage of a master protocol is flexibility and efficiency in drug development, consistent with FDA's goal of helping to make safe and effective drugs and drug combination treatments available to the public. A master protocol provides an opportunity to incorporate efficient approaches, such as a shared control arm and/or the use of centralized data capture systems to enhance efficiency.
>
> However, a master protocol also can create challenges in the conduct and analysis of the trial that, if not properly addressed, can increase risk to patients or delay the development of the drug**"** (ibid).

Study Design Complexity Could Compromise Research Subject Safety

> **"**Examples of potential challenges include the following:
>
> • Difficulty in attribution of adverse events to one or more investigational drugs can occur when multiple drugs are administered within various arms and the trial lacks a single internal control for those drugs.
>
> • With multiple drugs being studied across multiple protocols and investigational new drug applications (INDs), assessing the safety profile of any given investigational drug is difficult.
>
> • The presence of multiple study groups allows potential overinterpretation of findings, resulting in delays in drug development. For example, a biomarker-defined subpopulation could be identified, because of multiple comparisons, as a responder population based on ad hoc between-arm comparisons that prove to be false**"** (supra at pp. 3-4).

In a section titled "IX. Additional Regulatory Considerations," the guidance adds that:

> **"**Because of the complexity of master protocols and the need to avoid miscommunication that could compromise patient safety, sponsors should submit each master protocol as a new IND to FDA. For INDs that contain master protocols, sponsors should consider the following:
>
> • The master protocol should be the only trial that is conducted under the IND**"** (supra at p. 13). **{TBC}** ©

IRBs and Activities That Don't Have to Be Reviewed - Pt. 2

We continue here with our coverage of a new guidance issued by the federal Office for Human Research Protections (OHRP) titled "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements." As noted in last month's HRR, the main reason why the guidance is so useful for IRBs and researchers alike is that it describes in detail the activities that do not require IRB review. The potential savings in IRB personnel time and resources for the relevant "public health surveillance activities" would appear to be self-explanatory.

"Public health surveillance activities are deemed not to be research because HHS recognizes that the requirements of 45 CFR part 46 should not impede a public health authority's ability to accomplish its mandated mission to protect and maintain the health and welfare of the population(s) for which it is responsible**"** (guidance, page 4 of 10; on the Web at https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/activities-deemed-not-to-be-research-public-health-surveillance-guidance/index.html).[1]

More Than One Regulation May Apply to "Public Health Surveillance"

"[FN #1: 82 Fed. Reg. 7176.]

Other laws, regulations, policies, or standards may be applicable to the conduct of these activities, such as the Health Insurance Portability and Accountability Act: HIPAA Privacy Rule (45 CFR 160 and 164), and the World Health Organization guidelines on ethical issues in public health surveillance.

This explicit exclusion of public health surveillance activities from the definition of research does not mean that other public health activities that do not constitute public health surveillance activities, as described in 45 CFR 46.102(l)(2), are necessarily research subject to 45 CFR part 46.

Public health activities are varied, and may be neither research nor surveillance. Public health activities include such things as providing public service health messages or conducting vaccination campaigns. Public health activities that do not meet the definition of research under 45 CFR 46.102(l) are not subject to the 2018 Requirements, regardless of whether they constitute a public health surveillance activity as described in 45 CFR 46.102(l)(2).

The line between public health surveillance activities and research activities can be difficult to draw. The applicability of the public health surveillance activities exclusion depends on the purpose of the project, the context in which it is conducted, and the role of the public health authority.

Determining whether a project is a public health surveillance activity for purposes of 45 CFR 46.102(l)(2) requires familiarity with the language of the provision itself, the regulatory definition of a public health authority, the features of public health surveillance, and the details of the particular activity in question.

Because activities that constitute public health surveillance activities under 45 CFR 46.102(l)(2) are deemed not to be research, it is not necessary to consider whether they are systematic investigations designed to develop or contribute to generalizable knowledge**"** (ibid).

Which "Activities" Are Eligible For Exemption from IRB Review?

"*II. Determining what 'public health surveillance activities' are under the 2018 Requirements*

The 2018 Requirements do not prescribe any specific requirements for who determines whether projects do or do not constitute public health surveillance activities under 45 CFR 46.102(l)(2). Decisions about the applicability of 45 CFR part 46.102(l)(2) should be thoughtful and deliberate. There is no requirement that an IRB must make such findings.

This guidance discusses the three criteria set out in the 2018 Requirements for determining whether an activity constitutes a public health surveillance activity deemed not to be research:

- The activity must be a public health surveillance activity (45 CFR 46.102(l)(2));
- The activity must be conducted, supported, requested, ordered, required, or authorized by a public health authority (45 CFR 46.102(k) and 46.102(l)(2)); and
- The activity must be limited to that necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products) (45 CFR 46.102(l)(2))**"** (supra at pp. 5-6).

{TBC} ©

IRBs and "Broad Consent" For Certain Studies - Pt. 2

As we have discussed previously, the revised Common Rule on the protection of human research subjects (aka the "2018 Requirements"), set to become effective this month, contains dozens of new regulations and IRB-related issues - some of which have already become associated with new federal guidances (with many more to come).

For example, one relevant IRB concept is "broad consent," which is involved in one of the eight exemptions from the Rule and related IRB reviews. In particular, broad consent is involved in the storage, maintenance, and secondary use of identifiable private information and identifiable biospecimens.

In the April 2018 HRR we began coverage of a series of recommendations issued by the Secretary's Advisory Committee on Human Research Protections (SACHRP). These particular SACHRP recommendations were developed for IRBs and researchers on four different aspects of the revised Common Rule, and were submitted to the HHS Secretary as four attachments to a brief cover letter.

We began our HRR coverage with highlights from SACHRP's "Attachment A - FAQs Relating to Recommendations on Broad Consent." We resume here where we left off in the April 2018 HRR with the concluding portion of the IRB-review exemption issue in **FAQ #1: "Must the exemption at §_.104(d)(8) and the exemption at §_.104(d)(7) be used together?**" (see April 2018 HRR, p. 5).

Two Exemptions Don't Have to Be Used Together

"... secondary research use could be exempt under §_.104(d)(8) even if the storage and maintenance were not exempt under §_.104(d)(7) but instead had undergone full or expedited IRB review.

For example, a primary interventional study could include a separate banking component for identified biospecimens and data collected in the primary study, with a 'broad consent' covering the future uses of those biospecimens and data.

Such a study would undergo full IRB review and approval, and the maintenance and storage would not need to take advantage of the §_.104(d)(7) exemption, even though future uses would take advantage of the §_.104(d)(8) exemption [from IRB review].

Similarly, there could be identifiable biospecimens and data collected with 'broad consent' whose storage and maintenance would be exempt under §_.104(d)(7), although the investigator may prefer to submit (or may be required by IRB or institutional policy to submit) a protocol to the IRB for full or expedited review and approval, including a request for waiver of consent and authorization for each future use of those biospecimens and data.

This may be necessary in situations in which the future research use includes genetic testing or genomic sequencing, and applicable state law requires that such research be done only under an IRB-approved protocol, thus rendering impossible the use of the §_.104(d)(8) exemption.

Another situation in which the two exemptions would not be used together include a future research use in which investigators seek to return results to subjects, making the §_.104(d)(8) exemption unavailable, even though maintenance and storage of the identifiable data and biospecimens was conducted under §_.104(d)(7)**"** ("Attachment A - FAQs Relating to ...," April 11, 2018; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-faqs-relating-to-recommendations-on-broad-consent/index.html).

Previous IRB Approval Under Pre-2018 Regulations Will Remain in Effect

"Finally, a 'broad consent' adequate to receive the §_.104(d)(7) exemption for storage and maintenance may not have adequately expressed the future research use now planned, making the §_.104(d)(8) use exemption unavailable.

FAQ #2: For existing databanks and repositories of identifiable private information and identifiable biospecimens, would continued data and biospecimen storage of such materials and information, performed after the compliance date of the final rule be subject to pre-2018 Requirements or the final rule?

A protocol approved by an IRB, prior to the compliance date of the final rule, to establish a databank or repository would continue to remain in effect after the compliance date of the final rule, even if the protocol is later amended or modified. Data and specimen storage and maintenance conducted under a protocol approved before the compliance date of the final rule would not be affected by the final rule**"** (ibid). **{TBC}** ©

IRBs and Risks of Investigational *In Vitro* Diagnostic Studies - Pt. 9

We continue here with presenting key portions of FDA's current guidance on the special human subject risks associated with certain studies. The guidance is titled "Investigational IVDs Used in Clinical Investigations of Therapeutic Products - Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards."

In concluding our article on this topic last month, we presented a number of special risk areas for human research subjects in such studies (e.g., subject enrollment, dosing, monitoring, etc.). We continue here with:

> **"• Retrospective studies.** Retrospective studies involve the analysis of specimens after subjects are enrolled in the trial or the trial is complete. In most cases, if the investigational IVD result does not influence treatment, that IVD would be considered lower risk and may be exempt from most IDE regulation requirements if the criteria in 21 CFR 812.2(c)(3) are met ...." (guidance, December 18, 2017, p. 11 of 23; on the Web at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM589083.pdf).

Different Sources of Risk for Human Subjects

> "Prospective retrospective studies, where specimens are collected expressly for the purpose of retrospective analysis, would carry the risk associated with specimen collection occurring outside of standard patient care.
>
> Note that certain trial features do not inherently influence an investigational IVD risk determination. Among these are the size and the phase of the trial, the 'line' of therapy proposed for the investigational therapeutic product, and the potential access of patients to other trials.

3) How Investigational IVD Risk May Change During the Course of a Clinical Investigation

When an investigational IVD is NSR [Nonsignificant Risk] at the beginning of a clinical investigation but becomes SR [Significant Risk] at a later stage, or when a SR investigational IVD is introduced into a clinical investigation, FDA approval of an IDE application, in accordance with 21 CFR 812.20(a)(2) and 21 CFR 812.30(a), is required prior to use of the SR investigational IVD in the clinical investigation.

There are several ways in which an investigational IVD may be introduced into a clinical investigation or an investigational IVD's use may change during the course of a clinical trial.

- Safety and outcomes data, and other information gathered during the trial may change the risk of the investigational IVD.

  For example, if results from early subjects in the trial indicate more severe side effects or less improvement in a biomarker-positive population than expected, the assessment of risk from use of an investigational IVD to detect that biomarker may change.
- Adaptive clinical trial designs that incorporate pre-planned and conditional alterations in trial conduct may change the use of an investigational IVD as the trial progresses. Risk posed by altered use of the IVD should be considered.
- A new or amended study protocol for an existing investigational new drug application (IND) may introduce or alter the risk of an investigational IVD. For instance, a Phase 1 trial may not include an IVD or it may include an IDE or a NSR IVD" (supra at p. 12).

Ongoing Surveillance of Risks Is Vital

> "However, a later Phase 2 trial conducted under the same IND may add a SR device or may change the use of an investigational IVD in such a way as to make the IVD SR. In such a case, the sponsor would be required to submit an IDE application to FDA in accordance with 21 CFR 812.20; the investigational IVD could not be used in the Phase 2 trial until FDA approves the IDE application (21 CFR 812.20(a)(2) and 812.30(a)).

Ongoing surveillance during a clinical investigation is recommended to monitor the risk of the investigational IVD. For a SR investigation, the timing of an IDE application is at the sponsor's discretion and should be planned to allow sufficient time for FDA review before the use of the SR investigational IVD in the clinical investigation.

FDA recommends interacting with the applicable Center (CDRH or CBER) ... prior to initiating the first stage of the trial. This interaction may facilitate FDA review of a future IDE application if required and may provide the sponsor with greater predictability in regard to the IDE process" (ibid). **{TBC}** ©

In Congress

Advocacy Group Says OHRP "Can No Longer Be Trusted" - Pt. 6

As we have been reporting, the federal Office for Human Research Protections (or OHRP) has been accused by a number of groups and individuals as falling down on its mission of protecting human research subjects. Numerous reports have surfaced of researchers and IRBs failing to follow regulations on protecting human subjects and - presumably - exposing subjects to unnecessary risks.

These charges have been intensifying for more than ten years. In a letter to Senator Grassley (who then began investigating OHRP), the consumer advocacy group known as Public Citizen went so far as to state that OHRP **"**... can no longer be trusted to meaningfully enforce the federal human subjects protection regulations**"** (see last month's HRR, p. 8).

In concluding last month's HRR article on these claims, we presented two of OHRP's own written operating procedures regarding its mandated enforcement of subject protection regulations. We continue here with what HHS' own Office of Inspector General (OIG) found when it investigated OHRP, but we first present the two remaining OHRP SOPs of interest:

"• Posting on the agency's website each determination letter no later than 10 business days after the letter is issued to the institution [by OHRP after its evaluation of a problem]

• Once a compliance oversight evaluation is closed, making available upon request under the Freedom of Information Act all documents related to the evaluation

OHRP's written compliance procedures also stipulate an appeals mechanism under which a complainant (or institution) may request that the OHRP Director reconsider any determinations from a for-cause compliance oversight evaluation.

The OIG report's findings: For its July 2017 report, the HHS OIG analyzed data on OHRP's compliance activities for 2000 through 2015 as part of a congressionally requested assessment of OHRP's independence. The most striking observation presented in the report was the steep decline in the rate at which OHRP has initiated formal for-cause compliance evaluations in response to allegations of noncompliance since 2000.

For the four-year period from 2000 to 2003, the agency received a total of 487 allegations and initiated for-cause compliance evaluations for 195 (40 percent) of these**"** (Public Citizen letter to Senator Grassley, February 1, 2018, p. 2 of 4; on the Web at https://www.citizen.org/our-work/health-and-safety/letter-calling-senator-grassley-examine-ohrp-failure-adequately-protect-human-research).

Huge Drop in OHRP's Compliance Evaluations

"In contrast, for the four-year period from 2012 to 2015, OHRP received 456 allegations but initiated for-cause compliance evaluations for only 22 (5 percent) of these - a nearly 90 percent drop in the rate of initiating such evaluations.

Although some of this dramatic falloff is due to an erosion of resources as well as an increase in the proportion of allegations that are related to research deemed to be outside of OHRP's jurisdiction, much of the decline clearly reflects a fundamental - and troubling - change in how OHRP approaches its enforcement of the HHS human subjects protection regulations.

Indeed, OHRP explained to the OIG that 'it decided over the years to initiate fewer [for-cause] compliance evaluations both to better leverage its limited resources and to focus the evaluations on broad policy issues in protections for human subjects.' This explanation is disturbing for two reasons.

First, deciding whether to open a formal for-cause compliance evaluation based on whether a particular allegation raises 'broad policy issues' enshrines an approach to enforcement that by its very nature is arbitrary and capricious.

In particular, the public, complainants, and other stakeholders do not know when or on what basis OHRP has decided which policy issues are broad enough and of sufficient interest to use as a litmus test for deciding whether a particular substantive allegation warrants a for-cause compliance evaluation.

Nor do they know which broad policy issues OHRP is using to make these decisions at any particular time or whether the agency is applying them consistently and fairly.

Second, many substantive allegations of noncompliance do not raise broad policy issues but nevertheless often constitute the most serious types of noncompliance with the HHS human subjects protection regulations - such as conducting human subjects research without appropriate review and approval by an institutional review board or without the informed consent of the human subjects**"** (supra at pages 2-3). **{TBC}**

©

FDA Warning*

*See page 12 for HRR policy on investigative reporting

(Unless noted otherwise, recipients of a Warning Letter have 15 days to fix problems or explain how and when they will fix them. If not, they face sanctions with no additional warning and possible permanent disqualification from ever conducting research again with FDA-regulated products. This HRR feature includes Warning Letters sent to researchers, administrators, sponsors, and Institutional Review Boards.)

Warning Letter To: New York Researcher (Part 3)
Warning Letter Date: July 16-August 5, 2015
Investigation Period: February 19, 2016
Noncompliance In: Case History Requirements on Individual Human Subjects, and Failure to Follow Investigational Plan

* * *

Researcher Fails to Follow His Own Subject Selection Criteria

We continue this month with our presentation of the second of two human subjects research noncompliance areas discovered in this FDA investigation. The first area was the researcher's failure to keep accurate case history records about the research subjects who received the experimental drug.

The second area was the researcher's failure to follow his own investigational plan on human subject inclusion and exclusion criteria. We resume where we left off last month with:

"a. For Protocol ... [redacted], you failed to ensure that study subjects met the protocol inclusion and exclusion criteria before their enrollment. Protocol ... [redacted] specified that ... [redacted], confirmed by the Structured Clinical Interview for DSM-IV, Research Version, Patient Edition (SCID-RV/P), must be the primary psychiatric disorder present for the subject to be eligible for enrollment into the study.

However, ... [redacted] modules of the SCID were not completed at the screening visit for 13 subjects. Therefore, you failed to confirm a ... [redacted] diagnosis as the primary psychiatric disorder using the SCID-RV/P for 13 of the 14 enrolled subjects. Specifically:

i. For Subject 1, the ... [redacted] module of the SCID was not completed at screening on October 16, 2014. A notation, 'See ... [redacted],' was recorded in its place. Subject 1 was randomized on November 13, 2014.

ii. For Subject 2, the SCID was administered at screening on October 20, 2014. However, only a portion of the Brief Description of the Traumatic Events List of the ... [redacted] module was completed. Subject 2 was randomized on November 17, 2014.

iii. For Subject 3, the ... [redacted] module of the SCID was not completed at screening on November 13, 2014. A notation, 'See ... [redacted],' was recorded in its place. Subject 3 was randomized on November 17, 2014.

iv. For Subject 6, the ... [redacted] module of the SCID was not completed at screening on December 1, 2014. A notation, 'See ... [redacted],' was recorded in its place. Subject 6 was randomized on December 10, 2014.**"**

Researcher's Failure Covers Most Subjects

"v. For Subject 7, the ... [redacted] module of the SCID was not completed at screening on December 11, 2014. Subject 7 was randomized on December 15, 2014.

vi. For Subject 8, the ... [redacted] module of the SCID was not completed at screening on December 12, 2014. A notation, 'See ... [redacted],' was recorded in its place. Subject 8 was randomized on January 7, 2015.

vii. For Subject 10, the ... [redacted] module of the SCID was not completed at screening on January 16, 2015. A notation, 'See ... [redacted],' was recorded in its place. Subject 10 was randomized on January 20, 2015.

viii. For Subject 11, the ... [redacted] module of the SCID was not completed at screening on January 20, 2015. A notation, 'See ... [redacted],' was recorded in its place. Subject 11 was randomized on January 22, 2015.

ix. For Subject 12, the ... [redacted] module of the SCID was not completed at screening on January 26, 2015. A notation, 'See ... [redacted],' was recorded in its place. Subject 12 was randomized on February 2, 2015.

x. For Subject 13, the ... [redacted] module of the SCID was not completed at screening (date not indicated). A notation, 'See ... [redacted],' was recorded in its place. Subject 13 was randomized on February 4, 2015.

xi. For Subject 14, the ... [redacted] module of the SCID was not completed at screening on February 12, 2015. A notation, 'See ... [redacted],' was recorded in its place. Subject 14 was randomized on February 17, 2015.

xii. For Subject 15, the (b)(4) module of the SCID was not completed at screening on February 17, 2015. A notation, 'See ... [redacted],' was recorded in its place. Subject 15 was randomized on February 19, 2015.**"** **{TBC}** ©

OHRP Determination

*See page 12 for HRR policy on investigative reporting

Case: Alleged: Researcher failure to obtain informed consent; researcher failure to obtain IRB approval of study; multiple failures of IRBs; and researcher scientific misconduct (Part 24)
Investigating Agency: Office for Human Research Protections (OHRP) of the Department of Health and Human Services (HHS)
Case Included: Use of corticosteroids to treat serious lung disease (ARDS - Acute Respiratory Distress Syndrome) and sepsis
Case Commenced: September 15, 2004
Case Concluded: January 26, 2006

* * *

Researcher Keeps Objecting To Noncompliance Findings

At the close of last month's HRR article on this case, we pointed out that the investigated researcher continued his communications with OHRP even after OHRP had closed the case. As far as OHRP was concerned, according to OHRP's final letter to the university, all the allegations had been investigated, found to be either true or unproven, and rectified if relevant.

The involved researcher, however, clearly was not satisfied. As noted above, OHRP's case completion letter was dated January 26, 2006. If the researcher had any immediate response, it was not contained in the OHRP's files obtained by HRR, or not provided to us if it was in the case file.

Regardless, later that year, on October 21, 2006, the researcher emailed Captain Patrick McNeilly of OHRP with the following message.

"Dear Dr. McNeilly: I will be visiting and lecturing at the NIH Clinical Center on November 13-16 .... I wonder if it is possible for me to meet with you to discuss the [OHRP's] Division of Compliance Oversight report on my research and the discrepancies between the University report and the writing by the OHRP. I also wish to discuss other important related issues. Sincerely, ..." (9:38 am).

Two days later, in response, McNeilly sent the following email to the researcher.

"Dear Dr. ... : OHRP would be able to meet with you regarding your concerns. OHRP staff would only be available on Oct 13-15 due to other scheduling conflicts. In an effort to better understand the nature of your concerns, OHRP would request that you provide an agenda and a statement of your anticipated goals for meeting with OHRP" (October 23, 2006, 3:35 pm).

A few days later, on November 4, 2006, the researcher sent the following letter back to McNeilly.

"Dear Dr. McNeilly:

I am most grateful for the opportunity to meet. For me Tuesday November 14 in the afternoon would be most convenient if it agrees with your schedule. I would be most grateful if the matter could be dealt with strict confidentiality as I am seeking your guidance and direction.

I am including confidential documents; many of them refer to enclosures that will be made available on request."

Researcher Says His Lawsuit Led to University Prejudice

"In my meeting I wish to address two equally important issues.

1. The report submitted by the University in 2005 was partly prejudiced because of an ongoing lawsuit [filed by me].

It is my hope that the conclusion of the Report can be corrected in some of his [i.e., the university's respondent to OHRP's] statements and that [my] important research findings can be published.

It is my understanding that your office was made aware of the fact that your October 19, 2004 request for investigation was made while I had an ongoing lawsuit (enclosure 1) against the University for the handling of the allegations of misconduct against me.

I have concerns with the conclusions of your report as it appears in the Web. In particular with the sentence 'Due to the conflicting nature of the allegations and the ... [university's] report, OHRP is unable to make a determination regarding the allegations noted under item (4) above' [see the November, 2018, HRR for the university report's surrounding context regarding the fact that OHRP was 'unable to make a determination regarding the allegations'.]

This writing contrast[s] with the January 2005 ... [university's] own report (enclosure 1 ¶77).

Your [OHRP] investigation was initiated at the ... [redacted] request after the ... [redacted] received complaints from the former chair of the investigation committee at the ... [university] (enclosure 1 ¶71-72).

This by itself was a violation of due process since this individual signed a confidentiality agreement and already completed the investigation." **{TBC}** ©

In Court

This HRR feature includes lawsuits filed by former research subjects, researchers, and others over ***key research compliance issues***. Institutional Review Boards (IRBs), Institutional Biosafety Committees (IBCs), Conflict of Interest (COI) Committees, Data Safety Monitoring Boards (DSMBs) and Research Misconduct Committees may be involved. Members of such compliance committees often serve on more than one such committee.

* * *

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 21)
Key Issue(s): Possible IRB failure to protect human subjects, lack of informed consent, negligence, and violation of personal privacy by school officials (including IRB members)
Research Focus: Various effects of mandatory drug testing of student athletes compared to no drug testing ("Student Athletic Testing Using Random Notification" or SATURN study)
Court: U.S. District Court, District of Oregon (Portland (3))
Reference: Civil Case 02-CV-877-KI, June 28, 2002
Date: Case closed on April 22, 2004

Why Defendants Say Suit Should Be Dismissed

We continue here with more of the defendants' arguments on why the former research subject's Second, Third, Sixth, Seventh, Eighth, and Tenth claims should be deemed invalid by the court. In referring to these particular claims, the defendants said:

"Because all of these claims allegedly arise out of the Constitution (presumably the substantive Due Process Clause of the Fourteenth Amendment), plaintiff may only seek redress by way of §1983, and these claims should therefore be dismissed .... Fed. R. Civ. P. 12(b)(6), see also *Arpin v. Santa Clara Valley Trans. Agency* 261 F.2d 912, 925 (9th Cir. 2001) ('a litigant complaining of a violation of a constitutional right does not have a direct cause of action under the United States Constitution but must utilize 42 U.S.C. §1983').

Moreover, plaintiff cannot state a separate claim for *conspiracy* to violate her constitutional rights under §1983, since 'civil conspiracy is (merely) a vehicle by which §1983 liability may be imputed to those who have not actually performed the act denying constitutional rights.' *Barkauskie v. Indian River School Dist.* 951 F. Supp. 619, 539 (D. Del. 1996) ... (finding failure to state a claim for conspiracy to violate §1983 where plaintiff failed to prove any actual violations of §1983) ....

Therefore, plaintiff's Tenth Claim for Relief, as a separately stated claim for conspiracy to deny plaintiff her rights under the First and Fourteenth Amendments to the Constitution, should be dismissed.[9]

[FN #9: Again, as discussed ... [previously in our arguments,] plaintiff has also failed to state a claim for relief based on conspiracy, even under 42 U.S.C. §1983, since she has failed to make her conspiracy allegations sufficiently particular.]**"** ("Memorandum in Support of Defendants Oregon Health and Science University, Linn Goldberg, Diane Elliot, Kerry Kuehl, Esther Moe, and David MacKinnon's Motion to Dismiss ...." Nov. 4, 2002, Docket Document #20, pp. 12-13).

Agreements Do Not Confer Right to Sue

"V. First and Third Claims: No Private Rights of Action Exist under the Nuremburg Code, the Declaration of Helsinki, 45 C.F.R. §46, et seq., or 20 U.S.C. §1232h

No private rights of action exist under 20 U.S.C. §1232h, 45 C.F.R. §46, et seq., the Nuremburg Code, or the Declaration of Helsinki. Therefore, plaintiff's Third Claim for Relief (Breach of the Right to Be Treated with Dignity), and the allegations in the Complaint concerning OHSU, the Researchers and IRB's alleged violations of 45 C.F.R. §46, et seq., and 20 U.S.C. §1232h (which allegations have been incorporated into plaintiff's First Claim for Relief under 42 U.S.C. §1983), must be dismissed.

A. There is no private right of action available for alleged violations of the Nuremburg Code or the Declaration of Helsinki

There is no private right of action available for alleged violations of the Nuremburg Code or the Declaration of Helsinki.

The Nuremburg Code (the 'Code') is comprised of ten guiding principles regarding medical experimentation on humans, and was articulated by the Nuremburg Tribunals as part of a decision related to the non-consensual human experimentation by Nazi doctors on prisoners during World War II ....

The Declaration of Helsinki (the 'Declaration') was initially adopted by the World Medical Assembly in 1964, and has undergone several amendments. The Declaration has also been adopted by the U.S. Food and Drug Administration for purposes of regulating federal acceptance of foreign clinical trials of new drugs. 21 C.F.R. §312.120 (c)(4). The Declaration contains general guidelines for the conduct of biomedical research on human subjects ...." (pp. 13-14). **{TBC}** ©

Compliance Conferences & Courses - By Kathleen J. Maloney, M.Ed., Associate Editor

• **January 18, 2019,** Interactive Web Seminar (11:00 AM - 12:30 PM Eastern): **"Electronic Informed Consent Guidance: Regulatory Updates."** This Web-based seminar will be offered by Barnett International. Contact: Barnett Educational Services, 250 First Avenue, Suite 300, Needham, MA 02494 at 800-856-2556, or send a fax to 781-972-5441, or send an email to customer.service@barnettinternational.com.

• **February 28-March 1, 2019**, in Newport Beach, California: **"Pediatric Clinical Trials Conference."** This annual conference will be presented by the Society of Clinical Research Associates (SoCRA), with the meetings to be held at the Hyatt Regency Newport Beach. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **March 14-15, 2019**, in San Francisco, California: **"Oncology Clinical Trials Conference."** This course is presented by the Society of Clinical Research Associates (SoCRA), with the meetings to be held at the Holiday Inn Golden Gateway. Topics include: the role and function of a central IRB; the role and function of a data safety monitoring board; the process of reporting adverse events; and risk minimization through good clinical practices. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **March 20-21, 2019**, in Newport Beach, California: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP."** This conference will be presented by the Society of Clinical Research Associates (SoCRA), with meetings to be held at the Hyatt Regency Newport Beach. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **March 25-29, 2019**, in Lake Buena Vista, Florida: **"Clinical Research/Clinical Science Course."** This course will be presented by the Society of Clinical Research Associates (SoCRA), with the meetings to be held at the Wyndham Lake Buena Vista Resort. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send e-mail to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **April 4-5, 2019**, in Newport Beach, California: **"13th Annual Device Research & Regulatory Conference."** This conference is presented by the Society of Clinical Research Associates (SoCRA), with the meetings to be held at the Hyatt Regency Newport Beach. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **April 25-26, 2019**, in Scottsdale, Arizona: **"Hot Topics and Practical Considerations for Protecting Human Research Participants."** This course is presented by the Society of Clinical Research Associates (SoCRA). Meetings will be held at the Embassy Suites by Hilton Scottsdale Resort. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org. ©

HRR Policy on Investigative Reporting:** FDA **Warning Letters** and OHRP **Determination Letters** that are no longer timely, but contain valuable continuing education information on human subjects protection, appear in their respective sections - without identifiers. More recent Warnings or Determinations are presented as a protection for potentially involved research subjects or others possibly at risk from the cited study(ies) - perhaps with identifiers. Recent human subject protection incidents contain identifiers only if an allegation/inquiry/investigation about alleged research subject abuses/risks contains the views/arguments/findings/defenses/rebuttals of ***all involved parties.

Contact us at:
Human Research Report • PO Box 451117
Omaha NE 68145-6117 • USA
* * * * *
24/7 Toll-Free *Voice Mail* Phone: 800.786.5748
24/7 Fax: 402.895.2306
Email: Dennis@IRBusa.com
Web Site: www.IRBusa.com

Published each month since January, 1986
Web: www.IRBusa.com

HUMAN RESEARCH REPORT
Emailed to subscribers between the 7th and 11th of each month