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Human Research Report

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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SAMPLE ISSUE

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IRBs and New Recommendations On Expedited Reviews in Final Rule

On December 12, 2017, the influential federal Secretary's Advisory Committee on Human Research Protections (SACHRP) submitted a letter with attachments containing a new set of recommendations to Eric Hargan, Acting Secretary of the Department of Health and Human Services (HHS).

In this HRR article, we present key portions of the first of the two sets of SACHRP recommendations (the second set addresses the HIPAA Privacy Rule). Such recommendations often result in subsequent policy or regulatory requirements for IRBs, researchers, and research institutions. Hence, these recommendations give us a glimpse into the future.

"*SACHRP Recommendations on Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure under the Revised Final Rule*

Research that involves one or more of the following categories and is evaluated to be no more than minimal risk may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56. 110. A study is presumed to be minimal risk and thus eligible for expedited review if the study only involves categories described in this document, unless the reviewer determines and it is documented why the study involves more than minimal risk (§__.115(a)(8))**"** ("Attachment A," https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-december-12-2017/index.html, emphases added).

IRBs Must Decide on Level of Subject Risk

"The criteria for IRB approval of research as stipulated in 45 CFR 46.111 and 21 CFR 56. 111, including but not limited to requirements for informed consent and documentation of informed consent, as applicable, apply when expedited review procedures are used by the IRB.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB.

Evaluating if Proposed Activities are No More than Minimal Risk

Most research falling within one or more of the categories below will, ordinarily, present no more than minimal risk to subjects and will be eligible for review through the expedited review procedure. However, the IRB reviewer is required to evaluate all proposed research and consider whether the proposed research is more than minimal risk.

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.

NOTE #2: Articles may be continued in subsequent issues.

Also In This Issue

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In evaluating if the proposed research presents no more than minimal risk, an IRB reviewer should consider the nature of the study procedures, the implications of study findings for the subject (e.g., the results of genetic testing of blood samples), other study characteristics, and steps taken to minimize risk.

The IRB reviewer should also consider the characteristics of the subject population, including but not limited to age, health conditions, social or economic circumstances and experience in relation to the anticipated harms and discomforts.

The expedited review procedure may not be used, for example, when identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, educational advancement, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

In evaluating the risks, the IRB reviewer should consider only those risks that may result from the research (as distinguished from the risks of therapies subjects would receive even if not participating in the research)" (ibid, emphases added).

Categories of Research Eligible For Expedited IRB Review

"*Applicability*

A. Categories one (1) through fourteen (14) [as they appear in part below] apply to initial IRB review of research that has been determined to be no more than minimal risk.

B. Category fifteen (15) applies to continuing review of research previously approved by the convened IRB that does not otherwise qualify for expedited review.

C. The categories in this document apply regardless of the age of subjects, except as noted.

D. Research eligible for expedited review under §__110(b)(1)(i) must fit within one or more of the categories below.

E. Examples are intended to suggest the types of research activities and procedures that pose no more than minimal risk and may be approved using expedited procedures. However, the applicability of the category is not limited to the specific examples provided.

F. The expedited review procedure may not be used for classified research involving human subjects.

G. Unless an IRB determines otherwise, continuing review of research is not required for research eligible for and approved by expedited review in accordance with §__.109(f)(1)(i).

Research Categories

1. Research involving the use of drugs and medical devices only when condition (a) or (b) is met.

a. Research involving use of 'over-the-counter' drugs, when used within their approved indications and dosages, and exempt from the IND requirements of 21 CFR 312.

b. Research involving use of medical devices exempt from the IDE requirements of 21 CFR 812.[1]

[FN #1: In research involving the use of investigational devices that require a non-significant risk (NSR) determination, the determination should be made by the convened IRB. Continuing review of research where the FDA or the IRB has determined that a device is NSR may be eligible for continuing review under category 10(c).]" (ibid, emphases added).

Patient Sedation Cannot Be Used Solely for Research

"2. The collection of blood specimens for research purposes using techniques consistent with routine clinical practice to minimize pain and risk of infection and within the following limits: (a) from adults whose health will not be adversely affected by the blood draws who weigh at least 50 kg, the amounts collected should not exceed 550 ml in an 8-week period; or (b) from children[2] and other adults whose health will not be adversely affected by the blood draws, the amounts collected should not exceed the lesser of 150 ml or 3 ml per kg in an 8-week period.

[FN #2: Children are defined in the HHS (45 CFR 46.402(a)) and FDA (21 CFR 50.3(o)) regulations as 'persons who have not attained the legal age for consent to treatments or procedures involved in the research,

under the applicable law of the jurisdiction in which the research will be conducted.']

Examples: Finger stick, heel stick, ear stick, venipuncture, collection of blood from an indwelling peripheral venous catheter (not including a PICC line) placed for research purposes, or collection of blood from an indwelling catheter already in place for clinical purposes.

3. Prospective collection of biological specimens, excluding blood, for research purposes by noninvasive means and not requiring sedation for research purposes.

Examples: (a) tissues and fluids that the body produces continuously or sheds as a normal process (including hair, nails), which are collected in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation; (c) excreta and external secretions (including sweat, urine, stool); (d) uncannulated saliva; (e) placenta removed at delivery; (f) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (g) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (h) mucosal and skin cells collected by buccal scraping or mouth washings; (i) sputum collected after saline mist nebulization.

4. Prospective collection of biological specimens, excluding blood, for research purposes by minimally invasive means and not requiring sedation for research purposes.

Examples: (a) tissues from non-facial, non-genital skin punch biopsy with allowable local anesthesia and limited to 2mm in diameter and not requiring sutures; (b) specimens collected by swab (nasal, oral, urethral, vaginal, rectal); (c) teeth if routine patient care indicates a need for extraction**"** (ibid, emphases added).

Extension of Sedation Must Be Minimal Risk

"5. Collection of additional information or biological specimens, excluding blood, for research purposes during procedures already being performed for clinical purposes, provided the additional collection does not introduce more than a minimal increase in risk, pain or discomfort over that imposed by the underlying procedure. When extension of general anesthesia is required, it must meet the criteria for minimal risk.[3]

[FN #3: Extension of anesthesia time may be considered minimal risk when: the extension of anesthesia time is limited to no more than 15 minutes; the appropriate level of anesthesia has been achieved and the patient is determined to be clinically stable by an anesthesiologist uninvolved in the research protocol; the method/mode of anesthesia to be used is determined not by the research protocol but is in accordance with current standard clinical practice; the same anesthetic agents are utilized for the extension of time required for research; the same clinical care team responsible for administering and monitoring the anesthesia remain with the subject during the research procedure; and, the same level and frequency of monitoring will be maintained throughout the research procedures.]

Examples: (a) collection of additional bodily fluids and tissues (e.g., peritoneal fluid, bone marrow or cerebrospinal fluid); (b) tissue collected from pap smears; (c) collection of additional clinical information (e.g., vital signs, electroencephalography or echocardiography).

6. Collection of information for research purposes through noninvasive procedures and interventions routinely employed in clinical practice and not requiring general anesthesia or sedation**"** (ibid, emphases added).

Studied Activities Cannot Adversely Affect Subject's Health

"Examples: (a) physical sensors that are applied either to the surface of the body or used at a distance; (b) testing sensory acuity; (c) magnetic resonance imaging without use of contrast agent and using magnet and sequence parameters within accepted clinical use guidelines; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and transthoracic echocardiography; (e) measures of cognitive functioning; (f) exposure to ionizing radiation with a total effective dose not exceeding 0.1 mSv (the amount typically associated with a single chest x-ray) provided appropriate shielding techniques are employed.[4]

[FN #4: The US Nuclear Regulatory Commission's allowable annual exposure to individual members of the public is 0.1 rem (1 mSv) per year. 10 CFR 20.1031(a)(1) https://www.nrc.gov/reading-rm/doc-collections/cfr/part020/part020-1301.html.]**"** ©

IRB Reviews When eICs Are Used in Experiments

In concluding last month's article on IRBs and FDA's current electronic informed consent (eIC) requirements, we presented the FDA guidance's policy on HIPAA and research subjects' privacy - a key IRB review component. In particular, we ended with the guidance's Question 10 on how to help ensure the "privacy, security, and confidentiality" of the electronic system that includes the eIC.

We present here the FDA's related notation on regulatory applicability for Question 10.

> **"**[FN #15: The HHS Office for Civil Rights (OCR) administers and enforces the HIPAA Privacy Rule, which protects the privacy of individually identifiable health information and establishes an array of individual rights with respect to health information; the Security Rule, which sets national standards for protecting the security of electronic protected health information; and the Breach Notification Rule, which requires covered entities and business associates to provide notification following a breach of unsecured protected health information.
>
> Additional information about the HIPAA Rules is available on OCR's Web site at: http://www.hhs.gov/hipaa/.]**"** (guidance, December, 2016, p. 10 of 13, underline emphases added; on the Web at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf).

"Traditional" IRB Reviews Are Simply Not Enough When eICs Are Involved

IRBs need to be aware of the security features of any eIC system, since those features have a direct bearing on the protection of human research subjects. In turn, this means that the traditional review of the wording of the consent document, and a review of the procedures for administering said consent, are not enough when an eIC is used.

> **"**For example, the subject's information within an electronic system must be encrypted, unless the entity documents why encryption is not reasonable and appropriate in their specific circumstances and implements a reasonable and appropriate equivalent measure.
>
> **Q11. Can HIPAA authorizations for research, which are frequently combined with informed consent documents, be obtained electronically?**[16]
>
> [FN #16: For additional information, see the guidance for industry IRB Review of Stand-Alone HIPAA Authorizations Under FDA Regulations (available at http://www.fda.gov/regulatoryinformation/guidances/ucm122046.htm).]
>
> Yes. HIPAA authorizations may be obtained electronically, provided that the signature of the subject (or the subject's personal representative) is a valid electronic signature under applicable laws and regulations.[17]
>
> [FN #17: See the Electronic Signatures in Global and National Commerce Act (E-Sign Act) (Public Law 106-229) and 21 CFR part 11.]
>
> The Electronic Signatures in Global and National Commerce Act (E-Sign Act) (Public Law 106-229) addresses what constitutes a valid electronic signature and provides that a signature may not be denied legal effect because it is in electronic form.
>
> The HIPAA Privacy Rule requires that when a covered entity seeks an authorization from a subject (or a subject's personal representative), the covered entity must provide the individual with a copy of the signed authorization; this requirement also applies where a HIPAA authorization is obtained electronically.[18]
>
> [FN #18: See 45 CFR part 160 and subparts A and E of 45 CFR part 164.] ....
>
> **Q14. What eIC documentation does FDA require for submission with applications?**
>
> Investigational new drug application (IND) regulations do not specifically require submission of informed consent documents to FDA as part of an IND application ...." (supra at pp. 10, 14, underline emphases added).

Agency May Go Beyond the IRB's Review

> **"**... [However,] the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) may request submission of the informed consent form for review[19] under certain circumstances (e.g., when unusual known clinical toxicity is associated with the study drug or class of drugs; when the study population is particularly vulnerable; when the clinical investigation has significant potential for serious risks to human subjects; or for a postmarket safety clinical trial, required under section 505(o) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[20] to assess a serious risk).[21]
>
> [FN #19: See 21 CFR 312.23(a)(11).]
>
> [FN #20: 21 U.S.C 355(o).]

[FN #21: For additional information, see the draft guidance for IRBs, clinical investigators, and sponsors Informed Consent Information Sheet (available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm).]

Although all informed consent documents used in FDA-regulated clinical investigations must be reviewed by an IRB (see 21 CFR 56.103), there are situations in which CDER and CBER review of an informed consent in addition to IRB review is particularly important to determine whether a clinical investigation may safely proceed under 21 CFR part 312.

Investigational device exemption (IDE) regulations state that IDE applications must include copies of all forms and informational materials to be provided to subjects to obtain informed consent (see 21 CFR 812.20(b)(11)).

When FDA approval of an IDE application is required, a sponsor must not begin an investigation until the IDE application and informed consent materials have been reviewed and approved by FDA (see 21 CFR 812.20(a) and (b)).

The sponsor should submit to FDA the same eIC materials that will be presented to subjects to obtain eIC for their participation in the clinical investigation. For example, as part of an electronic submission to FDA, the sponsor should submit copies of all forms and informational materials including any videos, Web-based presentations, hyperlinks or other Web sites or podcasts ...." (supra at pp. 11-12, underline emphases added).

All Versions of IRB-Approved eIC Needed

"The sponsor should also submit any written information related to the clinical investigation that is provided to the subject on paper ....

The eIC materials should be provided in an electronic format acceptable to FDA, on an electronic storage device, or as a link to the eIC Web page that is accessible to FDA ....[22]

[FN #22: For additional information, see the guidance for industry Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm).

See also the guidance for industry and Food and Drug Administration staff eCopy Program for Medical Device Submissions (available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm370879.htm).]

Q15. What steps can be taken to ensure the system archives the eIC materials appropriately for FDA-regulated clinical investigations?

FDA regulations do not specify a preferred method for archiving documents; however, the eIC process should incorporate procedures to ensure that electronic documents can be archived appropriately and that all versions of the IRB-approved eIC can be retrieved easily. All procedures must be in compliance with applicable FDA regulations for electronic records.[23]

[FN #23: See footnote 10.]" (supra at p. 12, underline emphases added).

Materials to Be Available for FDA Inspection

"Q16. What materials or documents will FDA require during an inspection?

During inspections of clinical investigation sites,[24] FDA regulations require that FDA be granted access to records and reports made by the investigator, including site-specific versions of the eIC, the materials submitted to IRBs for review and approval, all amendments to the site-specific eICs, and all subject-specific signed eICs.[25]

[FN #24: See the information sheet guidance for IRBs, clinical investigators, and sponsors FDA Inspections of Clinical Investigators (available at http://www.fda.gov/regulatoryinformation/guidances/ucm122046.htm) and the FDA Compliance Program Guidance Manual (CPGM) 7348.811: Clinical Investigators and Sponsor-Investigators (December 8, 2008).]

[FN #25: Under the FD&C Act, FDA may inspect and copy all records relating to a clinical investigation (21 U.S.C. 374(a) (1)). See also 21 CFR 312.58, 312.68, and 812.145(b).]

These should be available at the site either in electronic or paper form. FDA reserves the right to review the content of the eIC program or informed consent document and the corresponding informed consent of the subject or the subject's LAR and the signature of a witness, where applicable, along with the date that the eIC was signed. Any updates to the documentation should also be available for review" (supra at p. 13, underline emphases added). ©

IRB Meeting Minutes and Joint Agency Guidance

We concluded last month's article on the recent joint HHS/FDA guidance on IRB meeting minutes by noting that IRB members can "attend" a meeting via an "alternative mechanism." That term refers to meeting, for example, via a telephone or video conference. We resume our coverage of the IRB minutes guidance with the following.

"An IRB may choose to appoint alternate members who may substitute for primary members for an entire meeting (e.g., when the primary member is not able to attend the meeting), or at any time during a meeting (e.g., when the primary member is not able to attend the whole meeting, or when the primary member has a conflicting interest and is recused from review of a particular study).

When an alternate member replaces a primary member at a convened meeting, the minutes must include the name of the alternate member in attendance (45 CFR 46.115(a)(2); 21 CFR 56.115(a)(2)). When an alternate member substitutes for a primary member due to a conflicting interest, the minutes should identify the name of the primary member for whom the alternate member is substituting, and state that this is the reason for the substitution**"** ("Minutes of Institutional Review Board (IRB) Meetings - Guidance for Institutions and IRBs," September, 2017, p. 4 of 13, emphases added; on the Web at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM470154.pdf).

Everyone's Name at Meeting Must Be Recorded

"IRBs may invite consultants to assist in the review of a particular study when expertise is required beyond or in addition to that available on the IRB (45 CFR 46.107(f); 21 CFR 56.107 (f)). If the IRB uses a consultant and the consultant is present at the convened meeting, the minutes must include the name of the consultant (45 CFR 46.115(a)(2); 21 CFR 56.115 (a)(2)), and should include a brief description of the consultant's expertise. In accordance with 45 CFR 46.107(f) and 21 CFR 56.107(f), the consultant may not vote with the IRB ....

If the IRB permits non-members and guests to attend a convened meeting (e.g., IRB support staff, the investigator whose study is being reviewed, study coordinator), then the minutes must record the name(s) of all such attendees (45 CFR 46.115(a)(2); 21 CFR 56.115(a)(2)).

The institution and the IRB may establish written procedures covering the use of alternate members, the use of consultants, and attendance of non-members and guests at a convened meeting. Such written procedures may help to ensure that those who attend an IRB meeting understand their role, and to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects.

2. Quorum

A quorum is the minimum number and type of IRB members that must be present at a convened meeting. In order to review proposed research at a convened meeting, a majority of the members of the IRB must be present, including at least one member whose primary concerns are in nonscientific areas (45 CFR 46.108(b); 21 CFR 56.108(c)). If a majority of the IRB membership is not present, or if a nonscientist is not present, then quorum has not been met.

The attendance information in the minutes assists in determining whether enough IRB members were present to constitute a quorum, whether the nonscientist was present, and whether proposed research received enough votes (i.e., a majority of those present) to be approved**"** (supra at p. 4, underline emphases added).

More Than One Way to Compute IRB Quorum

"IRBs often calculate majority by using the 'half-plus-one' technique. This technique works well for IRBs with an even number of IRB members. For example, if the total IRB membership is 10, then the majority is 6 (half of 10 is 5, plus 1 equals 6).

However, if the IRB has an odd number of members, then the majority should be calculated by taking half of the total number of IRB members, and rounding up to the next whole number. For example, if the IRB membership is 15, then majority is 8 (half of 15 is 7.5, and rounding up to the next whole number is 8).[3]

[FN #3: ... [The] regulations do not prohibit IRBs from having more stringent requirements ....]

A quorum must be maintained throughout the meeting. If quorum is lost during a meeting, then the IRB may not vote on proposed research (45 CFR 46.108(b); 21 CFR 56.108(c)). Because IRB members may occasionally enter or leave the room at various times during a convened meeting (e.g., arrive late, depart early, or leave the meeting temporarily), we recommend that the minutes provide sufficient information to indicate that a quorum is maintained**"** (supra at pp. 4-5, emphases added). ©

IRBs May Have to Brush Up On Research With Children

Changes are being considered by NIH for human subject experiments that involve children as the subjects. On December 1, 2017, NIH issued a notice about the current status of such developments that were put in place by the 21st Century Cures Act - enacted on December 13, 2016. That Act:

> "... includes new provisions requiring NIH to address the consideration of age as an inclusion variable in research involving human subjects, to identify the criteria for justification for any age-related exclusions in NIH research, and to provide data on the age of participants in clinical research studies.
>
> Furthermore, the Act requires NIH to convene a workshop of experts on pediatric and older populations to provide input on these issues, and taking account input received through the workshop, the NIH Director is charged with deciding whether any changes to NIH inclusion policies are needed" ("Notice of Intent to Revise the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects," NIH Notice NOT-OD-18-008, December 1, 2016, emphases added; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-008.html).

Federal Aim Appears to Be Increasing Pediatric Research

> "On June 1-2, 2017, NIH held a workshop on Inclusion Across the Lifespan to discuss barriers and opportunities for participation of children and older adults in clinical research studies" (ibid).

That workshop contained a number of presentations addressing the inclusion of young and older human subjects. For example, one presentation was titled "Inclusion Across the Lifespan" by Marie A. Bernard, M.D., Janine A. Clayton, M.D., and Dawn Corbett, M.P.H. Those presenters noted that the issue of including children as subjects, especially including more children in research, is not new.

One of the most relevant portions of the 21st Century Cures Act is Section 2038 ("Collaboration and Coordination to Enhance Research"). That section emphasizes the need to "... [include] relevant age categories, including pediatric subgroups" [and to] "allow for an increase in the number of subjects studied" (pp. 80, 81, emphasis added; on the Web at http://docs.house.gov/billsthisweek/20161128/CPRT-114-HPRT-RU00-SAHR34.pdf). ©

IRBs and Reimbursement of Some Clinical Trial Costs

The FDA has issued the final 14-pg. version of a previous draft guidance titled "FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) With Coverage Decisions: Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and ... [FDA] Staff."

> "This guidance modifies the FDA's current policy on categorization of investigational device exemption (IDE) devices, which assists the CMS in determining whether or not an IDE device should be covered (reimbursed) by CMS.
>
> On December 2, 2015, FDA's Center for Devices and Radiological Health (CDRH) and CMS's Coverage and Analysis Group (CAG) executed a Memorandum of Understanding (MOU) to streamline and facilitate the efficient categorization of investigational medical devices in order to support CMS's ability to make Medicare coverage reimbursement determinations for those devices" (82 Fed. Reg. 57460-57462 at p. 57460, December 5, 2017, emphasis added).

Reimbursement Eligibility Can Change Later

FDA points out that in recent years more and more IDE studies have been conducted in which the appropriate level of possible reimbursement for experimental use of medical devices is not clear. That is, it has not been clear whether such devices should be categorized as Category A ("Experimental") or Category B ("Nonexperimental/Investigational"), along with an appropriate determination of reimbursement potential by CMS.

> "The policy has been revised in order to allow FDA to consider information known about investigational devices as well, and provide FDA the flexibility to change categorization as more information regarding a device has been obtained.
>
> Therefore, while an innovative medical device may not be reimbursable during early-stage clinical trials, information gained during such studies now can be utilized to potentially help support a category change, and thus full reimbursement, for the device during subsequent studies" (supra at p. 57461, emphases added).

The guidance itself is on the Web at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM504091.pdf. For more information, contact: FDA's Owen Faris at 301-796-6356. ©

IRBs and the Application of Direct Versus Indirect Costs

The recent "NIH Policy on the Use of a Single IRB for Multi-Site Research Costs" is another NIH effort to assist IRBs and others in implementing the new "sIRB" policy for review of multisite trials. We begin our coverage of the policy with "Frequently Asked Questions (FAQs)":

"1. What are the 'cost principles' referred to in the NIH sIRB Policy?

The cost principles are described in regulations at 45 CFR 75 Subpart E, and are implemented by reference in the NIH Grants Policy Statement (Section 7.2). They establish standards for the allowability of costs, provide detailed guidance on the cost accounting treatment of costs as direct or indirect (F&A) costs, and set forth allowability and allocability principles for selected items of cost.

2. May direct costs be used to support administrative tasks of supporting a single IRB?

Direct charges for the salaries of administrative and clerical staff are allowable, but only if all of the following conditions are met: (1) administrative or clerical services are integral to a project or activity; (2) individuals involved can be specifically identified with the project or activity; (3) such costs are explicitly included in the budget; and (4) the costs are not also recovered as indirect costs**"** (no date; on the Web at https://osp.od.nih.gov/clinical-research/nih-policy-on-the-use-of-a-single-irb-for-multi-site-research-faqs-on-costs/).

Some IRB Costs Can Be Direct Costs

"Such charges must also meet the criteria for allowable costs described in 45 CFR 75.403. Under the NIH Standard Terms of Award, these costs do not require NIH prior approval as long as the above conditions and criteria are met, and the recipient has appropriate supporting documentation. Please see the NIH Grants Policy Statement Section 8.1.1.5.

3. Can the use of an independent (commercial) IRB as a single IRB be a direct cost?

Yes. Independent IRBs, which are not affiliated with a research institution, are neither included under another institution's F&A rate agreement nor do they have Federally negotiated indirect cost rate agreements of their own. Therefore, the fees charged by independent IRBs may be charged as a direct cost when they are serving as the single IRB**"** (ibid). ©

IRB Reporting Requirements Are Up for Federal Renewal

Comments are due by February 9 on procedures used by the Office for Human Research Protections (OHRP) that directly affect IRBs and their institutions. The procedures in question affect IRB Certification and Assurances. Specifically, OHRP is requesting:

"... an extension on a currently approved information collection by the Office of Management and Budget, OMB, on the Protection of Human Subjects: Assurance Identification/IRB Certification/Declaration of Exemption Form. That form is designed to provide a simplified procedure for institutions engaged in research conducted or supported by the Department of Health and Human Services (HHS) to satisfy the requirements of HHS regulations for the protection of human subjects at 45 CFR 46.103.

The respondents for this collection are institutions engaged in research involving human subjects where the research is supported by HHS. Institutional use of the form is also relied upon by other federal departments and agencies that have codified or follow the Federal Policy for the Protection of Human Subjects (Common Rule) which is identical to 45 CFR part 46, subpart A**"** (82 Fed. Reg. 58212, December 11, emphases added).

Opportunity to Comment on Reporting Burden

"Interested persons are invited to send comments regarding this burden estimate [an annual national total of 14,000 reporting hours for the 14,000 applicable entities] or any other aspect of this collection of information, including any of the following subjects: (1) The necessity and utility of the proposed information collection for the proper performance of the agency's functions; (2) the accuracy of the estimated burden; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) the use of automated collection techniques or other forms of information technology to minimize the information collection burden**"** (ibid, emphases added).

Anyone submitting comments about these IRB requirements should cite "Information Collection Request Title: 0990-0263-Extension Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption form."

Comments can be emailed to Sherrette.Funn@hhs.gov or phoned to 202-795-7714. ©

FDA Warning*

*See page 12 for HRR policy on investigation 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: California Researcher (Part 2)
Investigation Period: June 29 - July 17, 2015
Warning Letter Date: November 2, 2015
Noncompliance In: Experiments using riboflavin solution to treat keratoconus (progressive eye disease) or ectasia (distention of the cornea) as a researcher-sponsor

* * *

Researcher Pleads Ignorance of Requirements

We concluded last month's article on this investigation with FDA's conclusion that the researcher had enrolled subjects in at least seven different sites without submitting an IND to FDA. The researcher answered this charge with a written response on August 4, 2015. In turn, the FDA then told him that:

> **"** ... you indicated that you offered the surgical procedure for humanitarian/compassionate-use purposes, and that you submitted protocols and informed consent documents to an IRB. You stated that the IRB, the distributor of the riboflavin ophthalmic solution, and other ophthalmologists with whom you spoke did not inform you that an IND was required ....
>
> You acknowledged, however, that you should have contacted FDA about whether an IND was required. You stated that in the future, you will never conduct a clinical study without adequate due diligence, including discussion with FDA.
>
> Your response is inadequate because you have not yet submitted an IND application to FDA for the inspected study ....
>
> **2. You failed to ensure proper monitoring of the clinical investigations [21 CFR 312.50 and 312.56(a)].**
>
> FDA regulations require that sponsors ensure proper monitoring of clinical investigations, and ensure that their clinical investigators conduct the investigations in accordance with the general investigational plan and protocols contained in the IND. Our investigation found that you failed to ensure proper monitoring of the inspected study. The records associated with the inspected study do not indicate that proper monitoring was performed.
>
> In your August 4, 2015, written response to the Form FDA 483, you acknowledged that you depended on the surgeons to conduct the trial according to protocol, and that you did not have a monitor for this study. In addition, you acknowledged that you were not aware of all that was required of you as a sponsor.
>
> You stated that ... you will hire an experienced monitor to ensure that 'all the procedures/protocol in all sites are adequately monitored, all data collected, all consent procedures are followed, etc.' ...." (underline emphases added).

You Mean I Have to Keep Records Too?

> **"**Your written response is inadequate because you did not provide your proposed monitoring plan, including a timeline for when the experienced monitor would be hired. As a result, we are unable to determine whether your proposed plan appears sufficient to prevent similar violations in the future.
>
> In addition, please note that a sponsor may transfer its obligation to monitor a study to a contract research organization only, and any such transfer of obligations must be described in writing [21 CFR 312.52].
>
> **3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312. 62(a)].**
>
> As a clinical investigator, you are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. You failed to comply with this requirement. Specifically, you failed to maintain drug disposition records for any of the subjects at the seven study sites who underwent corneal cross-linking and received riboflavin ophthalmic solution in one or both eyes.
>
> In the August 4, 2015, written response to the Form FDA 483, you stated that you were not aware that you needed to maintain records of the disposition of the drug. You indicated that in the future, you will maintain drug disposition records for riboflavin ophthalmic solution.
>
> Your written response is inadequate because you did not address how you will maintain drug disposition records for the current study, or for future studies in which you serve as a clinical investigator. As a result, we are unable to determine whether similar violations will be prevented in the future." ©

OHRP Determination*

*See page 12 for HRR policy on investigation 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 11)
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

* * *

Several Phone Calls Over Investigation

In concluding last month's article on this case, we described an internal OHRP phone note recording that the investigated university's interim chancellor had called OHRP's Kristina Borror about the pace of the investigation. On that same day in late October of 2004, the chancellor sent the following letter to Borror to confirm the contents of that phone call.

> "Dear Dr. Borror: As we discussed by telephone this date, this is to acknowledge receipt of your October 19, 2004 letter requesting that ... [our] University of ... Health Science Center investigate allegations of noncompliance with HHS regulations for the protection of human research subjects ....
>
> The Health Science Center will certainly cooperate fully with your office and conduct a full and fair investigation of the allegations. However, in order to ensure a proper investigation, I respectfully request that the November 30, 2004 deadline be extended to January 31, 2005.
>
> Because of pending lawsuits related to this matter, I will need to take great care to identify the appropriate person(s) within or outside the Health Science Center to conduct this investigation. Once identified, the person(s) responsible for conducting the investigation will need sufficient time to become familiar with the files ....
>
> Under the circumstances, I do not believe a November 30, 2004 deadline is feasible. With the end of the academic semester and the holiday season approaching, I believe an additional 60 days will ensure a more thorough investigation. I would appreciate your favorable consideration of this request. Sincerely ...."

The next internal OHRP telephone log note shows that on the very next morning, at 11:43 a.m., the investigated Principal Investigator himself called Borror at OHRP. He was clearly unhappy and had questions for Borror about his research misconduct case, the allegation of noncompliance with human subject protection regulations, and his various options for defending himself and his research.

Researcher Wants to File His Own Complaint

> "... [The PI] called re: the October letter he was cc'd on re: his research. He asked how this came about. I said that we received a complaint about his research. He asked if he could get a copy of the complaint. I said no. I said he was free to file a FOIA request but it was not likely to be honored until after the case was closed.
>
> He said this complaint is old and he has been cleared. He asked if you [i.e., the PI] could file a complaint against them [i.e., the university]. I said that based on our conversation several weeks ago, it did not appear that he had any allegations of non-compliance with our regs, and we only have authority to investigate allegations of noncompliance with our regs.
>
> I said we [sic] is welcome to send any information that he thinks may help in our investigation. He said that his research has been maliciously attacked, is there no one to help him? I said that legal remedies may be his best bet" (telephone log of OHRP's Kristina Borror, October 27, 2004, emphases added).

A few days later, on November 8, 2004, Borror sent a short email to the interim chancellor. In that email she agreed to the university's request to extend the internal university investigation report deadline to January 11, 2005. Two days later, on November 10, 2004, the university's IRB sent the following notice to their College of Medicine.

> "The ... [university's] Institutional Review Board (IRB) has reviewed the allegations contained in the October 19, 2004 letter to Chancellor ... from the Office for Human Research Protections (OHRP). It is our understanding that the institution will evaluate these allegations and prepare, as requested, a response to OHRP.
>
> However, pending completion of the evaluation, the IRB has determined that the allegations require that new subject accrual to IRB project #6278 be suspended. This suspension is in keeping with ... IRB policy regarding ongoing studies in which allegations of non-compliance are received. This suspension will, of course, be reconsidered following completion of the Institutional evaluation" (emphasis added). ©

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, either simultaneously or, more often, at different times.)

* * *

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 8)
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

Alleged Violations of Constitutional Right

Last month we concluded our coverage of this case by presenting the "Sixth Claim for Relief - Lack of Informed Consent" filed against the university and its IRB. We resume our coverage here with the next claim that involves the Constitution.

"SEVENTH CLAIM FOR RELIEF - FOURTH AMENDMENT

107. Plaintiff hereby incorporates all of the above paragraphs as if each were set forth in full herein and further alleges as follows on behalf of herself and all others similarly situated.

108. At all relevant times, defendants were acting under color of state law.

109. Plaintiff Wade was forced to urinate into a cup and have her urine tested for drugs as part of the experiment and as a precondition for them [i.e., Wade and the other plaintiffs] to participate in sports.

110. Defendants' experiment constituted an unconstitutional search and seizure and served no compelling government purpose.

111. The actions of the defendants have caused plaintiff to suffer physical and emotional distress and have damaged plaintiff's reputation and breached her right to essential human dignity in the context of human subject research.

112. Also as a result of said unlawful acts, plaintiff has suffered humiliation, embarrassment, mental and emotional distress and anguish and loss of self-esteem.

113. As a result of all of which Plaintiff and other members of the class have been damaged in a sum in excess of $100,000.00, and they are entitled to an award of punitive damages for a sum in excess of $1,000,000.00.

EIGHTH CLAIM FOR RELIEF - RIGHT TO BODILY INTEGRITY

114. Plaintiff hereby incorporates all of the above paragraphs as if each were set forth in full herein and further alleges as follows on behalf of herself and all others similarly situated.

115. At all relevant times, defendants were acting under color of state law.

116. Plaintiff Wade was forced to urinate into a cup and have her urine tested for drugs as part of the experiment and as a precaution for her to participate in sports.

117. Defendants' experiment constituted an unconstitutional breach of plaintiff's right to bodily integrity" (underline emphases added).

IRB Members Charged With Negligence

"118. The actions of the defendants have caused plaintiff to suffer physical and emotional distress and have damaged plaintiff's reputations and have breached her rights to essential human dignity in the context of human subject research.

119. Also as a result of said unlawful acts, plaintiff has suffered humiliation, embarrassment, mental and emotional distress and anguish and loss of self-esteem.

120. As a result of all of which Plaintiff and other members of the class have been damaged in a sum in excess of $100,000.00, and they are entitled to an award of punitive damages for a sum in excess of $1,000,000.00.

NINTH CLAIM FOR RELIEF - NEGLIGENCE

121. Plaintiff hereby incorporates the allegations of the above paragraphs as if each were set forth in full and further alleges as follows on behalf of herself and all others similarly situated.

122. The IRB Defendants who approved the experiment had a duty to protect plaintiff and other members of the class from unethical research practices.

123. The IRB Defendants were negligent in approving the design of the experiment; in approving the informed consent documents; and in failing to appropriately monitor the informed consent process ...." ©

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

• **January 25-26, 2018**, in Houston, Texas: **"Clinical Site Coordinator/Manager Workshop: GCP for Coordinators, Research Associates, Study Nurses, and Site Managers."** This conference will be presented by the Society of Clinical Research Associates (SoCRA), with the meetings to be held at the Houston Marriott Medical Center. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292.

• **February 8-9, 2018**, in San Diego, California: **"Clinical Research Monitoring and GCP Workshop for Monitors, Site Coordinators, and Auditors."** This course will be presented by the Society of Clinical Research Associates (SoCRA). The meetings will be held at the Wyndham San Diego Bayside. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or send an email to Office@SoCRA.org.

• **February 14-15, 2018**, in Mesa, Arizona: **"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 Sheraton Mesa Hotel at Wrigleyville West. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send an email to Office@SoCRA.org.

• **February 22-23, 2018**, in San Antonio, Texas: **"Pediatric Clinical Trials Conference."** This conference will be presented by the Society of Clinical Research Associates (SoCRA), with meetings to be held at the Hyatt Regency San Antonio Riverwalk. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or email to Office@SoCRA.org.

• **February 27-28, 2018**, in San Diego, California: **"Rethinking What's Ethical: Impact of New Technologies & Innovative Care."** This Research Community Forum will be hosted by the federal Office for Human Research Protections and the University of California at San Diego, with planning assistance from other research compliance organizations. Meetings will be held at the Hyatt Regency Mission Bay. Contact: KLWoods@ucsd.edu, or CTPMO @ucsd.edu.

• **March 5-9, 2018**, in Miami Beach, Florida: **"Clinical Research/Clinical Science Course."** This workshop will be presented by the Society of Clinical Research Associates (SoCRA), with the meetings to be held at the Miami Beach Resort. 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 14-16, 2018**, in Chapel Hill, North Carolina: **"The Three I's (IACUCs, IBCs, IRBs) & Biosecurity: Promoting the Responsible Conduct of Research, Partnership, Ethics, Best Practices, and the Exploration of Current Trends."** This annual conference will be presented by the Massachusetts Society for Medical Research, Inc. (MSMR) and is cosponsored by the North Carolina Association for Biomedical Research, the FBI Weapons of Mass Destruction Directorate, and the Maine Regulatory Training and Ethics Center. The meetings will be held at The Carolina Inn. Contact: Lynne Walsh, Massachusetts Society for Medical Research, 73 Princeton Street, Suite 311, North Chelmsford, MA 01863 at 978-251-1556, or email to msmr@att.net.

***HRR Policy on Investigation Reporting:** FDA **Warning Letters** and OHRP **Determination Letters** that are no longer timely, but contain valuable continuing education information, appear in their respective sections - without individual identifiers. More recent Warnings/Determinations are summarized in feature articles - with identifiers - as a protection for anyone possibly at risk from the cited study(ies).

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