The Newsletter for IRBs & Research Ethics Committees

Human Research Report™

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRBs and New Proposal to Change Current Human Subject Regulations (#2)

As we introduced in our lead article of the February HRR, a current federal proposal would make significant changes to existing regulations on the protection of human research subjects.

More specifically, it would make major changes to 45 CFR Part 46, Subpart B ("Additional Protections for Pregnant Women, Human Fetuses[,] and Neonates Involved in Research"), as well as to other regulations.

We believe that these changes are relevant for all IRBs and researchers, including those who have nothing to do with this particular field of research.

Why? Because the core of these changes, as is clearly spelled out in the preamble to the proposed regulatory changes as published in the FEDERAL REGISTER, alters the key role of informed consent in research.

We add that informed consent is crucial for all human subjects research. As such, any modifications to consent regulations, no matter for what type of research, warrants extremely close scrutiny and deliberation before making any changes at all.

Informed Consent at Heart Of Proposed Regulations

As we said in a special communication to our subscribers, and we repeat here, HHS' publication of a mere 30 days public comment period would be laughable if it weren't so serious.

Hopefully, that comment period will be extended past the initial February 12 deadline. Regardless, input from the research compliance community at any point should be heeded.

We continue here to present primary portions of the proposal that we believe require careful and responsible deliberation. We leave the rest of the over 16,000-word federal proposal for readers to evaluate on their own.

We resume our coverage by presenting what we consider to be the most important parts of the regulatory change proposal. The FEDERAL REGISTER preamble's section that is involved is titled "*B. Research Involving Pregnant Women or Fetuses, §46.204.*"

"HHS proposes to add paragraph (k) to §46.204, which governs research involving

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 in brackets [ ] to make the material easier to read, to edit text or formatting, or to add an editorial comment.

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 {TBC}** in subsequent issues are marked at the end with **{TBC}**.

ALSO IN THIS ISSUE

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pregnant women or fetuses. Section 46.204 currently has two provisions which address abortion.

Section 46.204(h) states that '[n]o inducements, monetary or otherwise, will be offered to terminate a pregnancy.'

Similarly, §46.204(i) currently requires that '(i)ndividuals engaged in research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.'

Proposed paragraph (k) would require that the pregnant woman provide informed consent before the human fetal tissue obtained from the woman is used in HHS-funded research.

Subpart A of the Common Rule generally requires that, before research is conducted on a human research subject, the human subject must provide informed consent, but not for unidentifiable biospecimens.[41]

[FN #41: 45 CFR 46.116, 46.117.]" (86 Fed. Reg. 2620, January 13).

Not All Consent Provisions to Be Included

"As discussed previously, state law generally requires informed consent for participation in research, as well as informed consent for the donation of tissue for research.

In light of the serious ethical and moral considerations presented by the use of fetal tissue for research purposes, as well as to protect the interests of pregnant women (and the integrity of science), HHS proposes that the requirement for informed consent for tissue donation should apply to research involving human fetal tissue.

Because the fetus cannot provide informed consent, it is appropriate to obtain the informed consent of the woman from whom the fetal tissue would be obtained.

Such a requirement was included in the 2016 AMA Code of Ethics Opinion.[42]

[FN #42: AMA Code of Medical Ethics Opinion 7.3.5, available at https://www.ama-assn.org/delivering-care/ethics/research-using-human-fetal-tissue.]

For these reasons, HHS proposes to add these requirements in paragraph (k). HHS, however, does not propose to include in proposed paragraph (k) all statements that should be included in such an informed consent.

HHS further proposes that the requirement for such informed consent would apply with respect to donations of fetal tissue by women occurring after the effective date of the final rule" (ibid).

Clear Improvement: Using Plain Language in Consents

"HHS proposes that paragraph (k) would also establish specific requirements in order to meet informed consent requirements in this unique context:

• *The pregnant woman's consent must be documented on a written informed consent form that is signed by the pregnant woman and written in plain language that is clear and easily understandable.*

As explained in *Canterbury* v. *Spence,* true consent is the informed exercise of a choice, and that entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each.[43]

[FN #43: *Canterbury* v. *Spence*, 464 F.2d 772, 780 (D.C. Cir. 1972).]

This cannot occur if the pregnant woman's options are presented using complex medical jargon. For this reason, in promulgating its 2017 revisions to the Common Rule, HHS 'considered a growing body of literature that suggests informed consent forms have grown too lengthy and complex, adversely affecting their ability to effectively convey the information needed for prospective participants to make an informed decision about participating in research.'[44]

[FN #44: 82 FR 7211.]

For the pregnant woman's consent to be informed, the consequences of her decision must be written in plain language that is clear and easily understandable" (ibid). © {TBC}

IRBs and Hospital-Acquired Bacterial Pneumonia (#2)

We continue here with more tips for IRBs and researchers for experiments in a field receiving more attention due to COVID; namely, pneumonia associated with the increased use of ventilators for COVID patients.

The new final guidance from FDA is titled "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment." We resume where we left off last month with more recommendations on how to show efficacy in applicable clinical trials.

> "The Agency generally expects sponsors to conduct two adequate and well-controlled trials in HABP/VABP [hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia] to establish substantial evidence of effectiveness.
>
> Alternatively, a single adequate and well-controlled trial in HABP/VABP with confirmatory evidence (e.g., the results of a trial in another infectious disease indication) can provide substantial evidence of effectiveness[8]" (guidance, June, 2020, p. 3; on the Web at https://www.fda.gov/media/79516/download).

Ways to Measure Efficacy in Human Studies

> "[FN #8: See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).
>
> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.]
>
> Sponsors should discuss with the FDA the confirmatory evidence that would be used to support the efficacy findings from a single trial in HABP/VAB ….
>
> **B. Specific Efficacy Trial Considerations**
>
> *1. Trial Design*
>
> HABP/VABP trials should be randomized and double-blind when possible, comparing the investigational drug with an active control. In general, HABP/VABP trials will be designed as noninferiority trials.
>
> Another trial design is the add-on superiority design, in which patients receive either a placebo or an investigational drug added to standard-of-care antibacterial drug therapy.
>
> *2. Trial Population*
>
> For an indication for the treatment of HABP/VABP, the trial population should consist of patients who have HABP (regardless of mechanical ventilation) or VABP.
>
> The trial population should include at a minimum approximately 50 percent of patients who are on mechanical ventilation at enrollment (VABP/ventilated HABP).
>
> Sponsors interested in seeking an indication for HABP only should discuss the trial design and trial population with the Agency" (supra at pp. 3-4).

Important Inclusion/Exclusion Criteria for Human Subjects

> "The protocol can specify the use of a clinical severity scoring system to identify a trial population consisting of patients who have a sufficient severity of illness to maintain assay sensitivity for the all-cause mortality endpoint in a noninferiority trial (e.g., at least a 15 percent mortality rate).
>
> An example of a clinical severity scoring system is the Acute Physiology and Chronic Health Evaluation II.
>
> *3. Inclusion and Exclusion Criteria*
>
> a. Inclusion criteria
>
> Patients should have at least one of the following clinical features:
>
> • New onset or acute worsening pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (e.g., respiratory rate greater than 25 breaths per minute), expectorated sputum production, or requirement for mechanical ventilation
>
> • Hypoxemia
>
> • Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation or needed changes in the amount of positive end-expiratory pressure
>
> • New onset of suctioned respiratory secretions" (supra at p. 4). © {TBC}

IRBs and COVID: Statistical Considerations in Studies (#3)

With this article we conclude our coverage of an IRB topic sometimes overlooked but nevertheless crucial in applicable studies; namely the appropriate use of statistics to analyze a study.

As we've noted previously, lapses in accurate and appropriate statistics can invalidate a study and render the human subjects' participation essentially useless.

If subject risks are elevated, such failures or major weaknesses in statistical analyses are even more unjustifiable. Such risks during a pandemic are more worrisome yet.

Accordingly, we have presented the highlights of a FDA guidance titled "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency."

We resume where we left off in the October 2020 HRR with concluding portions of the guidance's section titled "B. Trial Mitigation and Analysis Strategies." This section addresses factors to consider when human subject enrollment and retention is severely lowered due to COVID.

When Study Participants Are Excluded

"(a) For example, all potentially impacted participants may be identified through the site location and randomization dates that are associated with endpoint ascertainment during the closure of the site.

If a significant number of participants are affected, this strategy may result in a significant loss of information, and alternative endpoint ascertainment methods and definitions can be considered (see item (6) below) or the enrollment for the trial can potentially be increased … to maintain statistical power.

(b) Similarly, if the closure of a site for a certain period of time greatly impacts trial-specified treatment for participants such that it is unlikely that any treatment effect can be observed, then it may be reasonable to exclude participants who were impacted during that period of time.

For example, if recently randomized participants are not able to obtain trial-specified treatment for an extended period of time for an investigational product whose hypothesized effect occurs only after sustained treatment, it may be reasonable to exclude from the analysis all participants potentially impacted.

Again, the decision to exclude participants should not use post-baseline participant information (e.g., on-treatment time), but instead use baseline information (e.g., site location and randomization date).

Such decisions should not be based on data that reveal treatment information and should be discussed with the FDA review division" (guidance, June, 2020, p. 5; on the Web at https://www.fda.gov/media/139145/download).

Choosing Appropriate Endpoints

"(c) Other well-established methods for addressing missing information rely on leveraging available participant information at baseline and post-baseline, including COVID-19-related information ….

6) Modifications to the definition and ascertainment of trial endpoints may be warranted to address the impact of COVID-19 on trial integrity and should be discussed with the relevant FDA review division.

Some potential modifications include the following:

(a) Using alternative ascertainment methods, such as replacing in-person endpoint ascertainment based on performance outcomes or interview-based clinician-reported outcomes with remote ascertainment ….

(b) Extending the protocol-defined window of time for performing the endpoint ascertainment or using an earlier or later planned ascertainment

(c) For a composite endpoint, including additional and clinically relevant components or removing components that cannot be ascertained

(d) For a binary endpoint that is based on a continuous or ordinal measurement, using the continuous or ordinal measurement as the endpoint" (supra at pp. 5-6). ©

IRBs and Protecting Subjects In Bioequivalence Studies (#1)

A recent FDA guidance is yet another in a series of new recommendations for IRBs, researchers, and others on facing particular challenges in studies due to the COVID-19 pandemic.

This set of tips focuses on bioequivalence studies, but IRBs and others will find elements here relevant to other types of studies as well.

"FDA is issuing this guidance to provide recommendations to prospective applicants of abbreviated new drug applications (ANDAs) on ensuring the protection of participants when resuming or initiating bioequivalence (BE) studies conducted to support the approval of an ANDA that have been disrupted during the COVID-19 public health emergency" ("Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency," January, p. 1 of 10; on the Web at https://www.fda.gov/media/145162/download).

Basic Research Requirements

"**A. Establishing Bioequivalence**

To receive approval for an ANDA, an applicant generally must demonstrate, among other things, that its proposed drug product is bioequivalent to the reference listed drug (RLD).[3]

[FN #3: See section 505(j)(2)(A)(iv) of the FD&C Act (21 U.S.C. 355 (j)(2)(A)(iv)) and 21 CFR 314.94(a)(7).

In general, to obtain approval of an ANDA for a generic drug, an ANDA applicant first must identify the previously approved drug product it seeks to duplicate (i.e., the RLD), and must show, among other things, that the generic drug is bioequivalent to the RLD.

A reference standard (RS) selected by FDA is the specific drug product that the ANDA applicant must use in conducting any *in vivo* BE testing required to support approval of its ANDA.

The RS, selected by FDA, is ordinarily the RLD. For ease of reference, this guidance document will only use the terms *RLD* or *reference product* when describing regulatory requirements and recommendations relating to BE.

For more information regarding the distinction between an RLD and RS, see FDA's guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (Oct. 2020).

For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.]" (supra at p. 2).

When Is "Close Enough" Actually Close Enough?

"The FD&C Act provides that a generic drug is bioequivalent to the listed drug if:

The rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.[4]

[FN #4: Section 505(j)(8)(B)(i) of the FD&C Act. See also section 505(j)(8)(B)(ii) and (C) of the FD&C Act; 21 CFR 314.3(b); 21 CFR 320.1; and 21 CFR 320.23(b).]

For most products, the focus of BE studies is on the release of the drug substance from the drug product into the systemic circulation.

During such BE studies, an applicant compares the systemic exposure profile of a test drug product to that of the RLD designated in FDA's *Approved Drug Products with Therapeutic Evaluations* (the ORANGE BOOK).[5,6]

[FN #5: See 21 CFR 314.3(b) defining reference listed drug and reference standard, 21 CFR 320.24 and FDA's guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (Oct. 2020).

FN #6: THE ORANGE BOOK is available at https://www.accessdata.fda.gov/scripts/cder/ob/.]" © {TBC}

IRBs and Patient-Reported Outcomes of Research (#1)

IRBs are beginning to be affected by a relatively new phenomena in human subjects research; namely, the emergence of "patient-reported outcomes" of study results. A recent draft guidance from FDA contains some useful tips for IRBs and researchers about this relatively new way of measuring the efficacy of new biomedical advances.

The importance of efficacy in research has traditionally been an important focus for IRBs in ensuring the safety and well-being of human research subjects. However, relying in part on the subject's report of study results to measure efficacy has not often received significant attention from IRBs or researchers. That is changing.

Therefore, we present in this article key highlights from the new draft guidance from FDA titled "Principles for Selecting, Developing, Modifying[,] and Adapting Patient-Reported Outcome [PRO] Instruments for Use in Medical Device Clinical Evaluation."

Although the focus of this particular FDA guidance is on research with medical devices, FDA is encouraging the use of PRO in studies on other FDA-regulated products as well. Hence, the growing importance of the use of PRO for IRB protocol reviews.

Human Subject Reports As Study Outcome Measures

> "A PRO instrument can be used in a clinical investigation to measure the effects of a medical intervention or changes in the health status of a patient ....
>
> Information from well-defined and reliable PRO instruments can provide valuable evidence for benefit-risk assessments and can be used in medical device labeling to communicate the effect of a treatment on patient symptoms, function, or quality of life" (85 Fed. Reg. 53821, August 31, 2020).

> "The U.S. Food and Drug Administration … encourages the collection, analysis, and integration of patient perspectives in the development, evaluation, and surveillance of medical devices. Patients' perspectives on living with their health condition and its treatment or management are most useful in medical device evaluation when they are relevant to the regulatory decision and reliably measured.[1]
>
> [FN #1: For more information, see FDA's guidance 'Patient Preference Information -- Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling,' available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.]
>
> Patient-reported outcome (PRO) instruments facilitate the systematic collection of how patients feel, function, and survive as valid scientific evidence to support the regulatory and healthcare decision-making process" (guidance, August 31, 2020, pp. 1-2; on the Web at https://www.fda.gov/media/141565/download).

Use of PROs in Clinical Studies

> "Use of PRO instruments is generally voluntary but may be specifically recommended in certain standards and guidances. PRO instruments can include patient diaries, visual analog scales (such as measures of pain severity), symptom measures, as well as multi-item, multi-domain questionnaires measuring aspects of health-related quality of life (HRQOL).[3]
>
> [FN #3: It is important to note that HRQOL is a multidimensional measure of the health and treatment experience of the patient, generally involving physical, social, and emotional domains and should not be used interchangeably with the term PRO, which is broader.]
>
> A PRO can be measured by self-report or by an interview, provided that the interviewer records only the patient's response. Symptoms and unobservable concepts known only to the patient (e.g., pain intensity and anxiety level) can be measured using PRO instruments.
>
> A PRO instrument can be used in clinical studies to measure the effects of a medical intervention or changes in the health status of a patient" (supra at p. 2). © {TBC}

SACHRP Recommendations For IRBs and Researchers

The federal Secretary's Advisory Committee on Human Research Protections (SACHRP) is the leading national body that develops recommendations for IRBs and others on better ways to protect human research subjects.

SACHRP's work has led to many new and revised regulations and practical tips for protecting human subjects.

* * *

IRBs and Financial Compensation For Human Research Subjects (#3)

At the outset of the SACHRP guidance that we are now studying, we find that the committee appears to be arguing against the tendency of many IRBs to avoid any kind of compensation for research subjects beyond bare minimums.

Defining such hesitations to be "problematical," SACHRP points out that compensation can be vital to both recruitment and retention of human subjects in important studies.

Instead, SACHRP considers many different pros and cons of participation compensation, beyond simply the overall dollar amount or other value of compensation.

In doing so, SACHRP has given the research compliance field, and IRBs in particular, much to think about when reviewing research protocols.

We resume here with more of the SACHRP's guidance contained in the section titled "When Payment May Constitute Undue Influence," as follows.

> "IRB approval of research should play an important role in minimizing the likelihood of adverse outcomes and promoting effective consent processes.
>
> Thus, the IRB's involvement should make offers of payment in research less concerning than payment offers might be outside the research context, where there may be no independent assessment of an activity's acceptability or support for the decision-making process.
>
> For every study, the IRB's first responsibility is to determine whether the risks of harm and potential benefits are appropriately balanced for the study's target population (i.e., those satisfying inclusion criteria and not meeting exclusion criteria). The IRB should consider whether payment is acceptable only after it is satisfied that the study is acceptable.
>
> With this approach, IRBs can protect typical participants in the target population from research that would be objectively harmful .... IRBs must also determine whether the informed consent process will provide clear and complete information about the study and support adequate consideration and comprehension of that information" ("Attachment A -- Addressing Ethical Concerns [Regarding] Offers of Payment to Research Participants," with a letter from SACHRP to Alex Azar, Secretary of Health and Human Services, September 30, 2019, pp. 4; on the Web at https://www.hhs.gov/ohrp/september-30-2019-letter-hhs-secretary.html).

Subjects' Right to Say "No"

"An adequate consent process enables participants to decline participation in research that would be subjectively harmful according to their own judgment of their interests, values, and obligations.

Thus, SACHRP takes the position that payment raises concerns about undue influence when it appears likely to inhibit potential participants' adequate consideration of and reflection about important study features, such as risks, burdens, and discomforts, and impair their understanding of the research and their participation in it.

Payments other than incentive payments are unlikely to have this effect. The mere fact that payment influences a decision to participate in research does not make that decision involuntary or that influence undue, even if an individual would not have chosen to participate without payment -- and even if the individual might have preferred not to participate if no payment was offered.

Decision-making is always influenced by many factors, and only factors that infringe on decision-making processes are problematic. When people adequately consider and understand what they are being asked to do and when what they are being asked to do is acceptable, there is no reason for ethical concern" (supra at pp. 4-5). © {TBC}

OHRP Investigation of IRBs and Researchers

Project Title: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Trial - ***Article #4***
Investigating Agency: Office for Human Research Protections (OHRP) of the Department of Health and Human Services (HHS)
Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)
Allegations: Violation of regulations on protection of human subjects, including inadequate informed consent and unjustificable risks to study subjects.

* * *

Researchers Make Claims About Strategy

We continue this month with more of the charges against IRBs, researchers, and the NIH by Public Citizen (PC) that a multisite human subjects study (CLOVERS) posed outrageous risks for the participants. We resume coverage with excerpts from PC's complaint letter to OHRP that:

> "(b) The investigators make claims of the liberal fluids strategy being used clinically but offer no evidence -- such as data from (1) an observational study or prospective survey conducted before the trial by themselves or others or (2) a systematic review of the scientific literature of relevant studies in this field -- to demonstrate that this management strategy is employed clinically by anyone for usual care of early septic shock.
>
> 2) The CLOVERS investigators did make several assertions implying that they consider the liberal fluids strategy to be an approximation of usual sepsis care. However, none of the CLOVERS investigators' assertions about this strategy can be substantiated by the information or references provided by the CLOVERS investigators in their protocol. In particular, we noted the following:
>
> (a) In a recently published report explaining the most current rationale for their trial,[5] the CLOVERS investigators asserted that the liberal fluids strategy will consist of IV fluid management 'similar to that of the usual care groups' in the following three recent large, well-documented sepsis trials: Protocolized Care for Early Septic Shock (ProCESS), Australian Resuscitation in Sepsis Evaluation (ARISE), and Protocolised Management in Sepsis (ProMISe).
>
> [FN #5: Self WH, Semler MW, Brown SM, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. Ann Emerg Med. 2018 May 9. pii: S0196-0644(18) 30315-9, doi: 10.1016/j.annemerg med.2018.03.039. [Epub ahead of print])" (in letter from Public Citizen's Dr. Michael Carome (Director, Health Research Group and a former OHRP official) to Jerry Menikoff, M.D., J.D. (OHRP Director), Aug. 28, 2018, p. 4; at https://www.citizen.org/sites/default/files/2446.pdf).]

PC Says Strategy Comparison Not Accurate

> "Our analysis found that the post-randomization early (first six hours) fluid and vasopressor management of subjects who were randomly assigned to the usual-care control groups of the ProCESS, ARISE, and ProMISe trials included fluid volumes that were smaller, administered far less rapidly, and frequently combined with vasopressor therapy compared with the CLOVERS liberal fluids group management strategy.
>
> By design, the CLOVERS liberal fluids group protocol administers to subjects with septic shock very aggressive fluid treatment and attempts to markedly limit the use of vasopressors -- making this strategy not usual care but unusual care.
>
> (b) The CLOVERS investigators also asserted that such a liberal fluids strategy dominates current emergency department care in the U.S., [a claim that] is based in part on the initial Surviving Sepsis Campaign (SSC) recommendations and early goal-directed therapy, and is encouraged by the SEP-1 Core Measure from the Centers for Medicare & Medicaid Services and The Joint Commission" (ibid). © {TBC}

FDA Warning

Warning Letter To: Houston, TX IRB (Part 5)
Warning Letter Date: September 24, 2012
Investigation Period: Ended on April 25, 2012
Noncompliance: IRB Members Repeatedly Failed to Follow Regulations; IRB Eventually Disbanded by FDA Order

* * *

FDA's Concerns Over IRB Keep Growing

We resume here with more results from FDA's investigation into the IRB whose days were obviously numbered. FDA told the IRB that:

"Prior to responding to the Warning Letter, you called the designated CBER representative on September 27, 2012[,] to discuss the Warning Letter and your proposed written response.

The CBER representative returned your call on September 27, 2012[,] and answered your questions pertaining to certain confidentiality issues, as well as questions relating to meeting minutes from 2011 that [you told us] were lost.

You responded to the Warning Letter in letters dated October 8, 2012[,] and October 19, 2012.

On November 8, 2012, CBER became aware that while the IRB was under FDA's [previous] restrictions, … [your IRB] had reviewed and determined the … [redacted by FDA] to be a … [redacted by FDA].

On November 13, 2012, the CBER representative called and emailed you requesting all documents reviewed and the meeting minutes supporting the IRB's November 7, 2012 … [redacted by FDA] for the … [redacted by FDA]. You responded in a letter dated November 14, 2012.

After reviewing your three letters, FDA continued to have serious concerns about whether … [your] RRC's [Research Review Committee's] proposed corrective action plans were adequate to bring the operations of the IRB into compliance with FDA regulations at 21 CFR Part 56. As a result, FDA requested a regulatory meeting to [discuss IRB] issues with you.

On February 22, 2013, FDA representatives and … [your] RRC held a regulatory meeting via videoconference to discuss and request additional clarification regarding … [your] RRC's corrective action plans to attain compliance, including the IRB's structured approach to maintain long-term compliance with federal regulations.

During the February 22, 2013[,] regulatory meeting, FDA expressed concern about your proposed corrective actions ... including the following:

- The implementation of the new … RRC SOP No. 104 *Application of Conflict of Interest*.
- Your conflict of interest as an active participant in both … [redacted by FDA] (a clinical research consultation service) and … [your] RRC (an Institutional Review Board).
- … [Your] RRC's failure to bring the IRB's membership into compliance with FDA regulations" (Sept. 16, 2014, pp. 1-2).

FDA Is Satisfied With Some IRB Improvements

"At the conclusion of the regulatory meeting, FDA requested the following: (1) documentation supporting … [your] RRC's updated proposed corrective actions; (2) revised Standard Operating Procedures; (3) updated membership and medical advisory core rosters; (4) training records; (5) copies of all signed Conflict of Interest Statements; and (6) a listing of all IRB activities since September 24, 2012, the date of the Warning Letter. You responded in letters dated March 18, 2013[,] and May 30, 2013.

The Center has reviewed your letters and finds acceptable your corrective actions for:

1. Item 2 on p. 2 of the Warning Letter, regarding the IRB's method of reviewing protocols and consent forms for pediatric subjects.
2. Item 4 on p. 3 of the Warning Letter, regarding the IRB's failure to determine that a pediatric study was in compliance with Part 50 Subpart D.
3. Item 5C on p. 5 of the Warning Letter, regarding the IRB's membership roster identifying each member's affiliation" (supra at p. 2). © {TBC}

In Court

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 47)
Key Issue(s): Possible IRB failure to protect human subjects, lack of informed consent, negligence, and violation of personal privacy by school officials (including by 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

* * *

Constitutional Amendments Central To High School Student's Lawsuit

We continue now with more of the plaintiff's arguments that her constitutional rights under the Fourth and Fourteenth Amendments had been violated by the researchers, despite approval of the study by the involved IRB.

These amendments involved human dignity, bodily integrity, privacy, and freedom from unreasonable government search and seizure.

> "As defendants [i.e., the university et al.] assert, the Oregon Court of Appeals addressed the constitutionality of drug testing in the [very same] SATURN experiment under the Oregon Constitution in October 2002.
>
> That court held that the plaintiff, an Oregon high school student-athlete, failed to demonstrate unconstitutionality of her school district's drug testing policy, but only because the plaintiff provided no evidence regarding the reasonableness of the drug testing policy. *Weber v Oakridge Sch. Dist.*, 2002 WL 31383053 at *16 (Or. App. Oct. 23, 2002).
>
> Indeed, Judge Schuman's concurring opinion forewarns that a future case involving an identical drug testing policy might be held unconstitutional if plaintiff would only put forward facts that demonstrate the policy's unreasonableness or base its case on an alternative legal theory. *Id* at *18. Judge Schuman states:
>
> ['] First, the majority's lucid and thorough opinion holds only this: the trial court did not err in concluding that the record plaintiffs made in this case (two affidavits) and the argument they relied on exclusively (the warrant requirement of Article I, section 9, of the Oregon Constitution does not have an 'administrative search' exception) do not establish that defendant's drug testing program deprives their daughter of a constitutionally guaranteed right to be free from unreasonable searches and seizure.
>
> More to the point, the majority opinion does not establish that random, suspicionless drug tests of high school student athletes are constitutional; it holds only that these plaintiffs did not put on a case proving that this program is unconstitutional[']" ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, pp. 5-6).

Current Case Is Precisely the One Predicted By Previous Court's Judge

> "['] With no deviation from the precedent that the majority opinion establishes, we could hold in a future case that some other student athlete drug testing program violates Article I, section 9, or that identical program, challenged differently, does so. *Id*.[']

This is that future case. Wade alleges facts as to the reasonableness of the same drug testing policy that was considered in *Weber*.

More specifically, this drug testing, implemented as part of an unethical experiment, and not to deter drug use, violated Wade's constitutional rights under the Fourth and Fourteenth Amendments to the United States Constitution.

Wade alleges that the experiment, which incorporates drug testing, is what abridges her rights to dignity and bodily integrity under the Fourteenth Amendment.

Wade also alleges that this experiment and the drug testing that is a part of it, which violates numerous federal regulations and has been shut down by the OHRP [federal Office for Human Research Protections], is not only clearly unreasonable and unconstitutional, but also intentionally intrusive, coercive, fraudulent[,] and retaliatory in nature." © {TBC}

Compliance Comment Deadlines & Notices

• **Department of Health and Human Services.** A comment deadline that we presented in last month's HRR ***has been extended*** by HHS.

The comment opportunity involved "Modifications to the HIPAA Privacy Rule to Support, and Remove Barriers to, Coordinated Care and Individual Engagement." The previous deadline for public comments was March 22. ***It is now May 6***.

We included this item in the March HRR because of the likelihood that ***some of the proposed changes could affect researchers working with human subjects and, by extension, to the IRBs that review and monitor such research***.

Although the announced aim of the HIPAA Privacy Rule changes was to enhance health care services to various patient groups, we believe that said modifications ***could easily impact how researchers (and associated IRBs) would handle privacy and confidentiality of private health information (PHI) in the future***.

HHS has stated that it intends to make such HIPAA Privacy Act changes to:

> "… support individuals' engagement in their health care, remove barriers to coordinate care, and decrease regulatory burdens on the health care industry while continuing to protect individuals' health information privacy interests" (86 Fed. Reg. 13683, March 10).

See the March HRR for details, or access the previous HHS proposal via http://www.regulations.gov by searching for Docket ID Number HHS-OCR-0945-AA00. It appeared in the FEDERAL REGISTER for January 21 at 86 Fed. Reg. 6446.

For details, contact: Marissa Gordon-Nguyen at 800-368-1019 or 800-537-7697 (TDD).

• **National Institutes of Health.** As we have reported before in the HRR, ***the issue of diversity and inclusion in research continues to be a major topic of interest for IRBs, researchers, and the research compliance field in general***.

We have discussed specific recommendations from federal agencies such as those issued by FDA on ways to increase diversity in the human subject population pools participating in studies.

However, the causes for a lack of diversity in human subjects' involvement, especially in clinical trials that may pose high risks, continue to remain difficult to solve. NIH has announced a specific funding approach to address these issues.

Titled the HEAL Initiative, this funding program appears as a "Notice of Special Interest (NOSI) regarding the Availability of Administrative Supplements to Support Strategies to Increase Participant Diversity, Inclusion[,] and Engagement in Clinical Studies."

With a funding application deadline of April 30 and a max budget of $375,000 per award, this competition is designed to address human subject diversity and inclusion challenges for participants "suffering from pain and opioid use disorder." The program title of HEAL stands for "Helping to End Addiction Long-Term."

> "This supplement program is ***not*** intended to support research on basic processes but rather to ***implement strategies to enhance stakeholder engagement and diversity and inclusion in HEAL clinical studies***.
>
> Activities proposed must be within the scope of the approved aims of the parent award" (NIH Notice No. NOT-NS-21-025, Mar. 5; on the Web at https://grants.nih/gov/grants/guide/notice-files/NOT-NS-21-025.html).

As a trans-agency notice, this funding opportunity has numerous NIH contact persons. See the above Notice for details.

• **Secretary's Advisory Committee on Human Research Protections.** The SACHRP scheduled a meeting for March 23-24 as a webcast. It was scheduled to be open to the public and to address the following ***human subjects protection issues*** on March 23:

> "… recommendations on ***Justice as an Ethical Concept*** in 45 CFR 46, followed by an expert panel discussion of draft recommendations on ***Mandatory Exploratory Biopsies in Research.*** The day will conclude with discussion of a new SACHRP topic, ***IRB Authority to Restrict Use of Data in Research***.
>
> March 24th will include presentation of ***Interactions between Sponsors, Clinical Trial Sites, and Research Subjects***, and lastly, ***Consideration of Risks to Bystanders in Research***" (86 Fed. Reg. 12194, Mar. 2).

For more information, contact: Julia Gorey, J.D., SACHRP's Executive Director, at 240-453-8141, or send an email to SACHRP@hhs.gov, or see their Web site at www.AAHRPP.org. ©

IRB Compliance Conferences & Courses

Readers unable to attend may still access proceedings and any other available conference and course materials

COVID-19 UPDATE: Conferences may be postponed or cancelled. Please check with Conference Contacts to verify latest schedule.

- **April 22-23, 2021**, in New Orleans, Louisiana: **"Hot Topics and Practical Considerations for Protecting Human Research Participants."** Topics to include: informed consent with vulnerable populations; research integrity; ethics and pediatric research; and the impacts of the revised Common Rule. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.
- **April 26-29 and May 3-6, 2021**, virtual conference: **"MAGI's Clinical Research vConference -- Spring 2021."** Topics include: 50+ sessions on clinical operations, quality and risk management, and regulatory compliance for IRBs and research administrators. Contact: MAGI's Norman Goldfarb at 650-465-0119.
- **April 28-30, 2021**, in Savannah, Georgia: **"2021 Device Research & Regulatory Conference."** The topics include: the role of IRBs in reviewing device research and FDA inspections of IRBs. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.
- **May 18-20, 2021,** Web Conference: **"2021 AAHRPP Annual Conference: Real Research in a Virtual World."** Topics include: health inequality and social justice in the time of COVID; ethics of emergency use authorization; ethical, regulatory, and research complexities of human gene editing; and data privacy. Contact: Conference Registrar, AAHRPP, at 202-783-1112, or send email to accredit@aahrpp.org.
- **June 15, 2021,** Interactive Web Seminar (1:00 PM - 2:30 PM Eastern): **"Informed Consent Procedure: Lessons Learned from Inspection Findings."** The topics include: FDA findings on noncompliance with informed consent requirements, and how to implement the correct informed consent procedures to avoid FDA Warning Letters and their consequences. Contact: Barnett Educational Services at 800-856-2556.

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