America's Oldest National Monthly IRB Newsletter

Human Research Report™

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRB Reviews, Pediatric Research Regulations, And Updates to Scientific Considerations (#1)

FDA has issued two new draft guidances, both of which address numerous ethical and regulatory aspects of research involving children as the participants.

We present here what we consider to be the key highlights that will likely impact IRBs that review such research.

However, the two guidances (together totalling over fifty pages) obviously contain more details than we can present in a single HRR.

Therefore, we will describe additional highlights in future HRRs as time and IRB-related events permit.

We note that neither guidance explicitly describes recommended IRB actions for pediatric research, beyond a few practical resource citations which we will quote for IRBs' use.

Instead, dozens of references to "safety and efficacy" requirements abound throughout the two guidances.

"Safety and Efficacy" Are Basic IRB Topics

As IRBs know well, subject safety and study efficacy are both integral research requirements that justify human subject participation in any experiment.

This is particularly true of vulnerable populations such as children. Therefore, we will describe the guidances' proposals that affect "safety and efficacy."

Both guidances were published in the May 18 FEDERAL REGISTER. The first guidance is titled "Pediatric Drug Development: Regulatory Considerations -- Complying With the Pediatric Research Equity Act [PREA] and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act [BPCA]."

> "This draft guidance, when finalized, is intended to provide recommendations to [the drug research] industry on complying with the pediatric study requirements under the Pediatric Research Equity Act (PREA), and to describe the process for qualifying for pediatric exclusivity and the protections that pediatric exclusivity offers under the Best Pharmaceuticals for Children Act (BPCA).

Combining discussion of PREA and the BPCA together in regulatory guidance em-

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

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

NOTE #3: Articles **T**o **B**e **C**ontinued in subsequent issues are marked at the end of the article with **{TBC}**.

ALSO IN THIS ISSUE

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phasizes the sponsor's need to consider both laws when developing pediatric drugs and biological products" (88 Fed. Reg. 31764, May 18).

The second guidance is titled "Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations."

"This draft guidance addresses selected clinical, scientific, and ethical issues involved in developing drugs, including biological products, for pediatric use when such drug products are subject to the Pediatric Research Equity Act (PREA) and/or the Best Pharmaceuticals for Children Act (BPCA)" (88 Fed. Reg. 31766, May 18).

Opportunity to Give Feedback to FDA

There is still time to influence the recommendations contained in these guidances. Comments for both are being accepted until July 17. More information on both guidances is available from Rosemary Addy of the FDA's CDER at 301-796-2200, or send email to pedsdrugs@fda.gov.

We begin with the following excerpt from the second guidance listed above (see "IV-A. Considerations Regarding Data in Pediatric Populations," subsection "4. Safety Information."

Safety Data Needed from Pediatric Studies

"Safety information from adult human studies and animal models may provide preliminary information regarding the expected safety profile of a drug in pediatric populations, but safety information from administration of the drug to children is almost always needed to establish safety in the pediatric population.

Adverse effects of a drug in pediatric populations may not be predictable based on the adult experience, particularly adverse effects related to behavior, cognition, or growth. Nonetheless, pediatric safety information that is available from different formulations of a drug, or from other closely related drugs within the same class, as appropriate, should be reviewed" (guidance, May, revision 1, p. 12; on the Web at https://www.fda.gov/media/168202/download).

The more legalistic approach of the first guidance described above sets the regulatory stage with its definition of the human subject group affected by the new recommendations, as follows.

Regulatory Definition Sets Study Parameters

"For purposes of pediatric drug development, FDA generally considers the pediatric population to include those patients from birth to younger than 17 years (i.e., birth through 16 years of age), and to include the subpopulation age groups of neonates, infants, children, and adolescents.

Consistent with International Council for Harmonisation (ICH) guidelines, FDA considers these subpopulation age groups to be divided as follows:

- Neonates: birth through 27 days (corrected gestational age)
- Infants: 28 days to 23 months
- Children: 2 years to 11 years
- Adolescents: 12 years to younger than 17 years

The BPCA defines pediatric studies to mean at least one clinical investigation in 'pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary [of Health and Human Services] may include preclinical studies.'

For purposes of satisfying the requirements of PREA, assessments of safety and effectiveness [or 'efficacy'] must be performed in all relevant pediatric age groups, unless the assessments are waived or deferred.

The BPCA and PREA are designed to work together to encourage the development of data to inform the safe and effective use of drugs in pediatric populations. Under PREA, pediatric assessments are required for drug products with a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration unless the drug is for an indication for which orphan designation has been granted" (guidance, May, Revision 1, p. 3 of 39; on the Web at https://www.fda.gov/media/168201/download). © **{TBC}**

IRBs and Decentralized Clinical Trials (DCTs) (#1)

Study closings and research shutdowns throughout the country were forced by numerous COVID-related quarantines. Even without that impetus, a clinical trial trend has been accelerating.

That trend is a movement away from traditional clinical trial settings to instances where distances may be involved between experimental sites -- possibly very remote distances.

This trend has raised new challenges for the IRBs that review such "decentralized" studies. Fortunately, a new FDA guidance offers useful tips for affected IRBs. The guidance is titled "Decentralized Clinical Trials for Drugs, Biological Products, and Devices."

> "This draft guidance provides recommendations for sponsors, investigators, and other stakeholders [e.g., IRB members] regarding the implementation of decentralized clinical trials (DCTs) for drugs, biological products, and devices" (88 Fed. Reg. 27900-27901 at p. 27900, May 3).

Same Human Subject Rules Still Apply

> "In this draft guidance, a DCT refers to a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites .... These trial-related activities may take place at the homes of trial participants or in local health care facilities that are convenient for trial participants ....
>
> FDA's regulatory requirements for investigations of medical products are the same for DCTs and traditional site-based clinical trials ....
>
> Specific issues related to the feasibility, design, implementation, or analysis of a DCT should be discussed early with the relevant FDA review divisions. Appropriate training, oversight, and up-front risk assessment and management will be key to implementing a DCT successfully" (guidance, pp. 2-3; see https://www.fda.gov/media/167696/download).

IRB Oversight Still a Regulatory Concern

It is well established that various elements of experimental design can affect IRB reviews besides the obvious ones of subject recruitment, retention, and participation. Accordingly, we will address such relevant components of DCTs in future HRRs and time and events permit.

However, in the present article we shall focus our preliminary coverage of DCTs on the most salient features of applicable human subject protection such as informed consent and IRB oversight.

> "Obtaining informed consent remotely may be considered as [a crucial] part of a DCT. Institutional review board (IRB) oversight is required to ensure [that] the process is adequate and appropriate" (supra at p. 10).

Electronic Informed Consent May Be Used

> "• Investigators may obtain electronic informed consent from trial participants at their remote locations provided that all applicable regulatory requirements regarding informed consent are met.[32]
>
> [FN #32: For FDA regulations about informed consent, see 21 CFR part 50 (including the elements of informed consent under 21 CFR 50.25 and the documentation of informed consent under 21 CFR 50.27).
>
> For additional information, see the guidance for IRBs, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (December 2016).]
>
> • With a DCT, the informed consent process must include notifying participants of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject.
>
> • The informed consent should describe who will have access to the trial participant's personal health information obtained during the DCT.
>
> • FDA recommends the use of a central IRB in DCTs to facilitate efficient review of the protocol, the informed consent documents, and other relevant trial-related information.[34]
>
> [FN #34: See 21 CFR 56.114 (for a description of arrangements related to use of a central IRB). For additional information, see the guidance for industry *Using a Centralized IRB Review Process in Multicenter Clinical Trials* (March 2006).]" (supra at pp. 10-11). © **{TBC}**

IRBs and Reaction to Changes In Pediatric Research (#3)

We continue this month with more of the national SACHRP's response to recent FDA proposals to modify pediatric research regulations.

These proposals will affect how IRBs review and approve/disapprove research with children.

We resume where we left off with last month's HRR article on this topic (see p. 5).

"SACHRP is pleased that the [FDA] Draft Guidance addresses the concept of component analysis ....

The concept of 'component analysis' is rooted in the deliberations of the National Commission ....

However, there has not been clear guidance specifically on this topic available to the regulated community" ("SACHRP Recommendations on Draft Guidance 'Ethical Considerations for ... IRBs,' in section titled 'Assessment of Risk for Interventions or Procedures with a Prospect of Direct Benefit,' " April 4; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/sachrp-recommendations-on-draft-guidance-ethical-considerations-clinical-investigations-medical-products/index.html).

When IRBs Must Use "Component Analyses" in Their Reviews

"Many sponsors and investigators are unfamiliar with component analysis, leading to confusion when IRBs make determinations about the permissibility of multiple research procedures and interventions in research with children.

This confusion can also extend to IRBs that do not routinely review clinical investigations involving children, as the term component analysis is not a defined regulatory term and is not otherwise described in Subpart D.

While the regulations at §50.52 and 53 describe the assessment of the risk to children that is 'presented by ***an intervention or procedure*** that does not hold out the prospect of direct benefit' (emphasis added), portions of the regulated community may not understand that this means that the review should be completed using component analysis" (ibid). © **{TBC}**

IRBs and Pediatric Studies of Drugs (#4)

There continues to be what we consider to be an extraordinary number of new IRB review proposals and revisions of past IRB guidances on protecting children as research subjects.

In this article, we continue from the May HRR (p. 5) by presenting key excerpts from a recent revised draft guidance from FDA. It is titled "General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products."

"Pediatric participants may be exposed to no more than a minor increase over minimal risk if, among other criteria, the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition (21 CFR 50.53(c)).

Thus, for a clinical investigation to be approved by an IRB under this category, the enrolled pediatric participant must have a disorder or condition that meets these requirements.

The FDA interprets 'condition' to include being at risk for the disease (disorder) based on, for example, epidemiologic, genetic, and other factors" (guidance, September, 2022, p. 9 of 25; on the Web at https://www.fda.gov/media/90358/download).

When "Minor Increase Over Minimal Risk" Cannot Be Shown

"Furthermore, sufficient empirical data regarding the risks of the proposed interventions or procedures should be available to ascertain that the risks are no more than a minor increase over minimal risk (21 CFR 50.53(a)).

If available, adult data (including dose-response information) should be considered for this purpose.

When there are not enough human data to adequately characterize the risk, then the intervention or procedure generally would not be considered to present no more than a minor increase over minimal risk because the risks of the intervention or procedure would not be known with sufficient accuracy.

The risks of any blood and/or fluid sampling procedures also must represent no more than a minor increase over minimal risk (21 CFR 50.53(a))." © **{TBC}**

Multi-Agency Review of Pediatric Research (#3)

We continue this month with more coverage of the FDA's guidance titled "Research Involving Children as Subjects and Not Otherwise Approvable by an IRB: Process for Referrals to FDA and OHRP."

We resume our coverage here by picking up where we left off in the June HRR (p. 4) with FDA's advice to IRBs about the documentation that they must provide to OHRP and/or FDA if they wish to review such research.

"The documents supporting the referral[13] may include information that, under certain circumstances, could be considered confidential and exempt from public disclosure.

[FN #13: Documents supporting the referral include, e.g., the research protocol, parental/guardian permission and assent forms, and IRB meeting minutes.]

This information may include trade secret information (TSI), confidential commercial information (CCI), or personal privacy information (PPI) (including personally identifiable information)" (in the guidance section titled "IV.B. Documents and Public Review," page 8 of 14, March; on the Web at https://www.regulations.gov/document/FDA-2022-D-0142-0002).

How Different Federal Agencies Will Handle IRB Information

"After obtaining any necessary agreements and permissions from the IRB and/or sponsor, as discussed below, and documents are appropriately redacted, the agency will publicly post the referral documents (on FDA's website, for referrals to FDA, and in a public docket, for referrals to OHRP) as soon as possible after the public announcement of the meeting in the Federal Register.

FDA-specific information: All FDA advisory committee members who are special government employees have access to nonpublic information in advisory committee briefing materials and are bound by the same confidentiality protections as all other government employees.

The PAC/PES [Pediatric Advisory Committee/Pediatric Ethics Subcommittee] members will be reminded that TSI, CCI, and PPI must not be revealed ...." (ibid). © {TBC}

IRBs and Safety Studies With Young Subjects (#2)

As we last covered in the May HRR (p. 4), safety issues predominate in research with neonates. Although sponsors are obligated to ensure subject safety in various ways, IRBs have the final review responsibility for protecting those same subjects.

Therefore, it would benefit affected IRBs to be aware of the subject safety issues that are involved.

The relevant FDA guidance is titled "Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development" (https://www.fda.gov/media/165239/download). We resume our coverage with excerpts from the guidance's "Section III. A., Determining the Need for Long-Term Neurodevelopmental Safety Evaluations."

"Sponsors should assess whether a long-term neurodevelopmental safety evaluation for neonates enrolled in clinical studies should be conducted. This assessment should be initiated early in product development and should be reevaluated as new information becomes available" (guidance, February, p. 4 of 11).

Risk Factors to Monitor in Neonatal Studies

"... *2. Patient and Population-Specific Considerations*

a. Neurodevelopmental vulnerability: The anticipated rates of developmental, behavioral, and sensory impairments are inversely related to gestational age and birth weight and differ significantly across various congenital or acquired conditions.

Sponsors should seek the most current data to understand background rates of specific long-term neurodevelopmental outcomes in the population of interest.

b. Disease state characteristics: The disease or pathophysiology of the condition under study (e.g., metabolic processes or conditions associated with compromised blood-brain barrier integrity or altered cerebral blood flow such as meningitis, hypoxic-ischemic encephalopathy or perinatal arterial ischemic stroke) may increase the risk for adverse neurodevelopmental outcomes. Sponsors should address disease-specific vulnerabilities in the proposed evaluation of neurodevelopmental safety" (pp. 4-5). © {TBC}

IRB Recommendations By the SACHRP

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. Here are more of their IRB recommendations.

* * *

Document Title: "Attachment B -- Deceased Donor Intervention Research (DDIR) 45 CFR part 46," (*Part #4*)
Document Source: Letter to Alex Azar II, Secretary, Department of Health and Human Services
Document Date: August 12, 2020
Available at: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/august-12-2020-attachment-a-nih-data-sharing-policy/index.html

* * *

IRBs and DDIR ... More to Come?

Last month's HRR article on this topic ended with our presentation of the second of ten IRB-related questions posed to SACHRP by OHRP regarding DDIR. We continue now with more of these discussions due to SACHRP's prediction of a projected increase in the use of DDIR throughout the nation, and possible effects on IRBs.

We continue with SACHRP's answer to OHRP's second question, as follows.

"*Discussion:* SACHRP considers that an IRB's approval of deceased donor intervention research (DDIR) will be affected as follows:

(i) the time period available to a transplant candidate to accept or reject an organ offer:

Yes, because this will affect the informed consent content and process.

(ii) whether a transplant candidate is likely to die without a transplant or alternative treatments exist (e.g., dialysis for patients with end stage renal disease):

IRBs routinely approve research in which the prospective participants have no standard of care options and may be facing death. The likelihood of death should not affect the IRB's approval of the research, except in so far as it may compromise an individual's decision-making at the time consent is sought.

Individuals on the transplant list are at risk of death from their underlying condition; the offer of a research organ may provide an early opportunity for intervention, and refusal should not change their priority on the transplant list."

IRBs and "Risk of Death" Factor

"Thus, a refusal of a DDIR organ does not change an individual's risk of death from where it stood before the research offer, and it should not be considered a risk of the research (unlike any risk of death that may arise from the research intervention on the organ).

That being said, there is never a guarantee of an organ offer, and the IRB must acknowledge that a prospective participant's decisions will be significantly affected by the choice between acceptance of an immediate and potentially life-saving offer and deciding to continue to wait.

This is particularly true because for many DDIR protocols, the risks of harm from participation, although greater than minimal, may well be lower than the risks of death or increased disability arising from waiting longer for a standard organ."

Patient's Likelihood of Participating

"***(iii)*** the likelihood that transplant candidates will receive other organ offers, including offers of organs not subject to the same interventions:

This could affect an individual's decision whether to accept a DDIR organ. It is an important aspect of consideration of alternatives to participating in research. However, it is not clear how the availability or unavailability of other organs should affect the IRB's approval determination.

Certainly, individuals who are unlikely to timely receive another organ offer will be motivated to accept a research organ. As in (ii), this should not affect the IRB's approval of the research but will need to be considered in the process of obtaining informed consent.

Should DDIR become more common, it is also possible that approval of a research study could affect the supply of unmanipulated organs. That is, growth in approved DDIR could decrease the general availability of standard, unmanipulated organs, thus decreasing the likelihood that anyone on the

transplant list would be offered a non-research organ.

The potential for such an impact must be evaluated by the IRB or a committee charged with scientific review in the context of organ transplantation.

(iv) the fact that any organ offered for transplantation, whether subject to a research intervention or not, must be individually accepted by a transplant candidate:

It is not clear what this question [posed by OHRP] is intended to mean, nor why this circumstance should be regarded as specific to organ transplantation."

Proposed "Two Step" Consent Process

"Clinical consent (i.e., individual acceptance) is required for any surgical intervention unless there are circumstances that make it impractical or impossible, and affirmative research consent is required before a participant receives a research intervention -- a requirement that is subject to even more restrictive constraints than apply to clinical consent.

The challenge to IRB approval of DDIR arises from the particular context of this organ offer process, rather than from the requirement that an offer be accepted or declined.

Question 3. How practicable would it be for investigators to implement the two-step consent process proposed by the NAM? Specifically, is the second step of the proposed consent process feasible to implement given that it would occur at the time the organ is being offered to the transplant candidate?

Discussion: The step one discussion of DDIR is practicable by any standard, because it can feasibly be added to existing general education about transplantation. This general education discussion, which begins when potential transplant recipients are in the process of committing to wait for an organ, already includes education about organs that, for various reasons, might be less desirable than standard organs (they might pose a risk of infecting the recipient, or might be expected not to last as long as a standard organ ....)."

"Step Two" Could Be Coercive

"Potential recipients are educated generally about the reasons an organ might be designated as nonstandard and are told that they can choose not to receive some or all such offers but may change their decisions at any time.

Similarly, general education about DDIR organs and about being a research subject in DDIR could easily be provided during the step one discussion, and that information could be revisited and updated during clinical visits while the potential recipient is waiting for an organ offer.

When any organ is offered, including any nonstandard organ, information about that specific organ is provided in the step two organ offer discussion.

This second step, which occurs at the time of organ offer, is severely time constrained and made under circumstances that could be construed as unduly influential, or even coercive, because the possibly life-saving clinical offer of an organ is contingent on agreement to participate in research."

"IRBs Will Face Real Difficulty" In DDIR Informed Consent Process

"Further, this step is likely to be conducted over the telephone by a transplant coordinator who is not an investigator on the DDIR protocol, raising additional barriers to provision of sufficient 'opportunity to discuss and consider' participation.

For all these reasons, it would be difficult for this step alone to meet traditional ethical and regulatory requirements for information, comprehension and voluntariness, but consent regulations require that, absent regulatorily specified exceptional circumstances, potential participants be informed of the particulars of a specific research protocol at the time they must decide whether or not to participate.

Thus, it is this problematic second step in the process described in the NAM report that must satisfy the regulatory requirements for consent.

It may be practicable for clinicians or investigators to have the conversation that constitutes the second step in the NAM process, but the IRB will face real difficulty in determining that this conversation, while adequate for clinical consent, fulfills the regulatory requirements for research informed consent as usually interpreted." © {TBC}

OHRP Investigation of IRBs and Researchers

Project Title: Human Research Protections Under Federalwide Assurance No. 4952 (New York University Grossman School of Medicine) (*Part #5*)
Investigating Agency: Office for Human Research Protections (OHRP) of the Department of Health and Human Services (HHS)
Allegations: "Not-for-cause" investigation of overall human subjects protection system becoming "for cause" following concerns of National Institute of Mental Health (NIMH)
Reference: OHRP letter of March 21, 2022, to Imad Alsayed, M.D., Vice President, Clinical Research Operations and Regulatory Affairs; from Lisa Buchanan, MAOM, CIP, OHRP's Director of Compliance Oversight

* * *

"Corrective Action Plan" Becomes Goal

We continue here with more of the "corrective actions" that NYU undertook to address multiple findings of noncompliance.

"OHRP determined that the NYU HRPP appropriately identified and managed the serious human subject protections problems involving the principal investigator, including development of a corrective action plan.

In order to assess those issues, OHRP posed questions and shared many concerns with NYU about the six NIMH protocols led by the principal investigator.

The topics included informed consent, changes in the protocol without IRB approval, failure to follow OHRP reporting requirements of unanticipated problems, and altering of records to minimize the seriousness of certain study problems."

Principal Investigator Resigns

"1. In 2017, OHRP asked NYU to provide the status of all the principal investigator protocols, research data, and research files, including but not limited to, what information and guidance was provided to subjects that were involved in these protocols; and

2. A detailed report of corrective actions or improvement efforts to NYU's Human Research Program derived from OHRP's site visit observations and NIMH audit findings.

This report should include, but not be limited to, NYU's investigator audit or monitoring program, investigator training, IRB member training, procedures to ensure that investigator-initiated protocol changes are reviewed and approved by NYU IRB, procedures to ensure that consent was properly obtained from subjects as part of approved research protocols, and procedures for reporting unanticipated problems involving risks to subjects or others and non-compliance.

IV. OHRP's Resolved Concerns

Corrective actions taken by NYU after the June 2015 site visit as described in their letter to OHRP dated March 1, 2017[,] are outlined below:

1. After the principal investigator resigned from NYU , all his protocols were suspended for new enrollment by the NYU IRB.

The Chair and Research Vice-Chair of the NYU Department of Psychiatry assumed principal investigator responsibilities for all these protocols."

Former Subjects Informed of Noncompliance

"By assuming direct oversight of these protocols, they became responsible for all follow-up with subjects and reporting to the NYU IRB of any newly discovered protocol deviations and potential safety issues.

Simultaneously, the NYU IRB directed for-cause audits for all these protocols, then reported to and reviewed by the NYU IRB as reportable new information, which in turn was reported to OHRP, NIMH .... [sic]

The NYU IRB also required that subjects in affected studies be notified about the noncompliance, the principal investigator's departure, and the new principal investigators.

Updated NYU Policies and Tools

Several NYU IRB policies and tools were updated to enhance protection for human subjects. NYU ensured that their policies were consistent with the June 20, 2011, 'Guidance on Reporting Incidents to OHRP.'

Additionally, NYU developed and implemented training materials for this policy, including a checklist to reflect updated definitions of terms pertaining to the reporting of unanticipated problems. This checklist was then used as a reference tool during all IRB meetings." © {TBC}

FDA Warning

Warning Letter to: Mark H. Merrill, President and CEO, Valley Health, Winchester, VA (Part #1)
Investigation Period: January 29, 2013, to February 1, 2013
Warning Letter Date: May 9, 2013
Noncompliance: IRB failure to follow two federal regulations on protecting human subjects

* * *

IRB Expedited Review Procedures Were Faulty

This Warning Letter followed the FDA's investigation and in-person discussions between an unnamed official in FDA's Baltimore District Office and the health system's personnel. This followed FDA's issuance of its Form FDA 483 ("Inspectional Observation").

The following describes the health system's first area of noncompliance with human subject protection regulations.

"1. Failure to follow FDA regulations regarding the expedited review procedures. (21 CFR 56.110(b)(2))

The FDA regulations for IRBs require that, under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced IRB members designated by the IRB chairperson."

Conditions for Valid Expedited IRB Review

"The regulations state that the IRB may use the expedited review procedure to review either or both of the following: (1) some or all of the research appearing on the FEDERAL REGISTER list of categories of research that may be reviewed by the IRB through an expedited review procedure and found by the reviewers to involve no more than minimal risk; and (2) minor changes to previously-approved research.

Your IRB is in violation of this regulation, which does not extend to significant risk device studies currently under an IDE. These studies did not meet the criteria of minimal risk and the changes in the protocol were not minor.

Therefore, they were not eligible for expedited review according to the FEDERAL REGISTER list of research categories that may be reviewed by the IRB through an expedited review procedure."

Protocol Reviewer Did Not Have Expertise

"Examples of deficiencies include, but are not limited to, the following:

• For the study entitled ... [redacted by FDA] your IRB approved the protocol amendments #6 and #7 and revised the informed consent under expedited review. The changes included the ... [redacted by FDA] to the list of potential adverse events to study subjects.

... [redacted by FDA] are serious medical conditions that could affect the risk to study subjects and represent a major change in the research and should not be reviewed using the expedited review procedure.

Furthermore, your IRB allowed Ms. Deborah Moore, IRB Manager, to approve the protocol amendment involving the ... [redacted by FDA] as an adverse event under expedited review.

Ms. Moore does not possess the experience and background to perform this critical task. Major changes in research should be reviewed by a full IRB board whose members have the necessary diversity and expertise to evaluate these changes.

This is critically important for a complete and adequate review of research and to ensure the protection of human research subjects."

Expedited Review Was Not Appropriate

"• For the study entitled ... [redacted by FDA], your IRB approved the protocol and informed consent amendments II and III under expedited review that allowed the ... [redacted by FDA] and the ... [redacted by FDA] in the study.

These amendments, especially the use of additional devices, represent major changes in the research. Your use of the expedited review procedure was not appropriate because it precluded your IRB from conducting a thorough review of these changes to identify any additional risks to subjects.

This is a critical step in ensuring that appropriate human subject protection measures are in place to help mitigate those risks." © **{TBC}**

In Court

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (*Part 67*)
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

* * *

Officials' "Immunity" Under Fire

We continue here with a deeper examination of just how far a government employee's "immunity" extends when a lawsuit is involved.

"The issue before this Court with respect to the defendant government officers' qualified immunity is whether those government officers' conduct, in implementing the SATURN experiment, clearly violated either Wade's Fourth Amendment rights, or any of her rights under the Fourteenth Amendment, at the time of the violation" ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, p. 31).

Dominant Role of Informed Consent in Case

"At least with respect to unlawful searches and seizures [as the plaintiff's attorneys argued earlier], the law was clear and established that government officials cannot implement a drug testing policy without first establishing that there is a drug problem and that the drug testing policy is a reasonable solution to that problem.

Also, the law regarding informed consent of subjects in an experiment could not be any clearer. It is regulated by federal statute and to make playing in sports contingent on participating in the experiment involving drug testing not only violated federal regulations but is violative of a subject's rights to dignity and bodily integrity as described above [see previous HRRs]" (ibid).

Random Urinalyses Are OK Except When ...

"Defendant relies upon *Vernonia Sch. Dist. 47J v. Acton*, 515 U.S. 646 (1995) and *Board of ed. of Independent Sch. Dist. No. 92 of Pottawatomie Cty v. Earls*, 122 S. Ct. 2559 (2002), to illustrate that the defendants' alleged violations of the Fourth Amendment are not 'clearly established' because both decisions upheld random student urinalysis drug testing as constitutional whether or not the schools can prove that there is a drug problem.

However, the Supreme Court in both cases made it patently clear that suspicionless drug testing would not be constitutional if implemented for anything other than to deter drug use in a school with a drug use problem. Here, none of the schools were testing the urine of their student athletes until SATURN, through OSHU, paid for those tests" (pp. 31-32).

Key Role of Experiment in Lawsuit

"In *Vernonia* and *Earls*, informed consent was not an issue because there was no experiment. Here, it cannot be disputed that the purpose of the drug testing was not implemented to deter drug use. The purpose of the drug testing was to determine whether or not the drug testing actually deters use.

At a minimum, under the facts as alleged in the Complaint, the government individuals named are not entitled to immunity based upon clear and well-established constitutional principles. Moreover, there are no duly enacted statutes or ordinances upon which the defendant individuals relied, however, there is clear and well established law under the Fourth Amendment to be free from unreasonable searches and seizures.

[Next, HRR presents an additional charge brought against the university and others.]

4. Defendants' actions constituted an unlawful conspiracy under 42 U.S.C. §1983.

In order to prove conspiracy between private parties and the government under §1983, an agreement or meeting of the minds to violate constitutional rights must be shown. See *Woodrum v. Woodward County*, 866 F.2d 1121 (9th Circ. 1989)." © {TBC}

IRB Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** Comments are ***due by August 25*** on a new draft guidance titled "Psychedelic Drugs: Considerations for Clinical Investigations."

"Because interest in the therapeutic potential of psychedelic drugs has been increasing and designing clinical trials to evaluate these compounds presents unique challenges, FDA has developed this draft guidance to present foundational aspects for sponsors to consider ....

This draft guidance provides general considerations for sponsors developing psychedelic drugs for treatment of medical conditions (e.g., psychiatric disorders, substance use disorder) and discusses ***considerations for clinical investigations*** using psychedelic drugs ...." (88 Fed. Reg. 41407, June 26).

"This guidance applies to clinical trials that will be conducted under an investigational new drug application (IND), including such clinical trials (e.g., ***research or academic studies***) that are ***not*** intended to support marketing applications.

The principles in this guidance are intended to ***support the ethical conduct of clinical trials*** as well as to ensure the integrity of the trial and the reliability of the results ....

Because this is an emerging area of drug development, there is limited experience as to the configuration of programs that may support approval of a psychedelic drug. Rather than providing specific recommendations on study design, this guidance will present foundational constructs that all sponsors, ***including academic sponsor-investigators***, studying the therapeutic potential of psychedelic drugs should consider" (guidance, June, p. 2 of 11; on the Web at https://www.fda.gov/media/169694/download).

For more information, contact: Kofi Ansah of FDA's CDER at 301-796-4158.

• **Food and Drug Administration.** Comments are ***due by September 5*** on a draft guidance titled "E6(R3) Guideline for Good Clinical Practice."

"The draft guidance was prepared under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The draft guidance outlines modernized Good Clinical Practice considerations to guide thoughtful design and ***responsible conduct of clinical trials in a manner that ensures participant safety*** and the reliability of trial results.

This draft guidance encourages innovation, focuses on quality, and establishes proportionate and risk-based approaches for conducting clinical trials, while minimizing unnecessary complexities" (88 Fed. Reg. page 37257, June 7).

The lengthy and detailed guidance itself is available on the Web at https://www.fda.gov/media/169090/download. For more information, contact: Amy Chi of FDA's CDER at 240-402-0992, or send email to amy.chi@fda.hhs.gov; or Diane Maloney of CBER at 240-402-7911, or send an email to diane.maloney@fda.hhs.gov.

• **Secretary's Advisory Committee on Human Research Protections.** The SACHRP scheduled a virtual public meeting for July 19-20. The first day's agenda includes a discussion of a topic which we predict will soon be a nationwide issue for all IRBs; namely, ***whether IRBs are actually effective at what they are charged to do***.

IRB "effectiveness" was a significant issue discussed in a recent GAO report (GAO-23-104721) titled "Institutional Review Boards: Actions Needed to Improve Federal Oversight."

See our April HRR (pp. 1-2) for more details about this recent report.

"This [discussion] will be followed by commentary on the FDA draft guidance, *Decentralized Clinical Trials for Drugs, Biological Products, and Devices*, in addition to discussion of recommendations that address the ***ethical conduct of decentralized clinical trials in human subjects research more broadly***.

Discussion of both topics will continue on July 20, in addition to commentary on the recently released draft HHS guidance, *Frequently Asked Questions: Limited Institutional Review Board Review and Related Exemptions*" [see our July HRR (pp. 1-3) for details on this recent guidance] (88 Fed. Reg. 42086, June 29).

For more information, contact: Julia Gorey, J.D., SACHRP Executive Director, at 240-453-8141, or send an email to SACHRP@hhs.gov. ©

IRB Compliance Conferences & Courses

Readers unable to attend may still access available conference/course materials

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

• **September 11 - October 2, 2023,** Virtual Webinar Series, Four Presentations (beginning at 1:00 pm, ET, Mondays). **"iSRA Research Compliance Ethics[,] and Integrity Intensive."** Topics include: internal institutional controls; IRB/IACUC/IBC responsibilities and requirements for researchers; authorship and responsible publication practices; data management; conflicts of interest; and risk assessment and management. Contact: Conference Registrar, Society of Research Administrators International, at 703-741-0140, or send email to registration@srainternational or info@srainternational.org.

• **September 14, 2023,** Virtual Workshop (9:45 am - 4:15 pm, ET). **"2023 OHRP Exploratory Workshop: Old Trips, New Destinations - Exploring the Ethical and Practical Considerations of Psychedelics Research."** The topics include: ethical and practical considerations for psychedelics research with the goal of promoting an open and grounded discourse on how to conduct research that is inclusive and protective of participants. Contact: OHRP's Yvonne Lau, Education Director, at 240-453-8236, or send email to Yvonne .Lau@hhs.gov.

• **September 26-27, 2023,** in Ann Arbor, Michigan. **"OHRP Research Community Forum: Making a Difference in Human Subjects Research - Empowering Participants, Engaging Communities, and Protecting Data."** Meetings to be held at the Michigan League. Topics include: reviewing research under the Common Rule; participant-centered informed consent; the new NIH Data Management and Sharing (DMS) policy and the role of HRPPs; supporting community engagement; diversity, equity, and inclusion in IRB reviews and IRB oversight; current OHRP policy initiatives; ethical considerations in data sharing; consent form innovations; best practices and IRB reviews of social and behavioral research; and data protection with Certificates of Confidentiality. Contact: Sana Shakour via email to sanashak@umich.edu.

• **October 14-18, 2023,** in Seattle, Washington: **"SRA International 2023 Annual Meeting: Breaking Barriers - Together Towards Tomorrow."** This annual conference is held by the Society of Research Administrators (SRA), with the meetings to be held at the Hyatt Regency Seattle. The topics include: ethics of human research; peer reviews; mentor/trainee responsibility and development; collaborative research ethics; scientific misconduct; research ethics education programs and requirements; institutional liabilities and corrective action planning; and data ownership and sharing. Contact: SRA International at 703-741-0140, or send an email to info@srainternational.org, or see their Web site at www.srainternational.org. ©

Dennis Maloney, Ph.D., is the founding Editor of the Human Research Report. He earned his degree in Experimental Psychology (with Honors). He has authored or edited over 200 works (reference book, textbook chapters, newspaper column, academic journal articles, etc.), and won over $20 million in grant awards. More of his works are available on the Web at FocusSurveys.com and at MyLuckyPenny.com.

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