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IRBs and FDA's Advice on How To Cope With Coronavirus (#4)

We continue here with more recent updates for IRBs, researchers, and others on the effects of COVID on certain types of human subjects research. Our focus in this article is on the newly revised guidance from FDA titled "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards."

This article adds new information beyond what we've already covered in previous HRRs (e.g., see the May, June, and October 2020 issues).

We resume below where we left off in the October 2020 issue; namely, with the remainder of a key section from the introductory portion of the guidance subtitled **"C. For all trials that are impacted by the COVID-19 public health emergency."**

What Happens When COVID Disrupts Trial?

"Sponsors should describe in appropriate sections of the clinical study report (or in a separate study-specific document):

1. Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.
2. A listing of all participants affected by the COVID-19 related study disruption by unique trial participant number identifier and by investigational site, and a description of how the individual's participation was altered.
3. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Robust efforts by sponsors, investigators, and IRBs/IECs to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. As stated above, FDA recognizes that protocol modifications may be required, including unavoidable protocol

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 **T**o **B**e **C**ontinued **{TBC}** in subsequent issues are marked at the end with **{TBC}**.

Also In This Issue

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deviations due to COVID-19 illness and/or COVID-19 control measures.

Efforts to minimize impacts on trial integrity, and to document the reasons for protocol deviations, will be important" (Guidance, rev. December 4, 2020, p. 6 of 35; on the Web at https://www.fda.gov/media/136238/download).

The body of the guidance is relatively brief, but the subsequent Q&A Appendix is extensive and filled with practical tips for researchers and the IRBs that review relevant protocols. The initial Q&A #1 sets the stage for the detailed useful recommendations, as follows.

Monitoring Threats to Safety of Subjects

"Q1. What are some of the key factors that a sponsor should consider when deciding whether to suspend or continue an ongoing study or to initiate a new study during the COVID-19 public health emergency?

A1. Central to any decision should be ensuring that the safety of clinical trial participants can be maintained. Sponsors, in consultation with clinical investigators and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), should assess whether the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial.

Such decisions will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease under study in the trial.

As part of this assessment, sponsors should carefully consider the following aspects of clinical trial conduct when deciding how or whether to proceed with a clinical trial:

• Assessing whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

• Assessing the continued availability of the clinical investigator/sub-investigators to provide oversight of the trial and properly assess and manage safety issues that may emerge" (supra at p. 8).

Study Personnel Must Have Enough Supplies to Monitor Subject Safety

"• Assessing whether there will be sufficient clinical trial support staff given the evolving COVID-19 situation and its impact on staff availability. Are there appropriately trained staff that could be available to handle the expected tasks? Is there adequate equipment and materials for clinical trial support staff?

• Assessing whether clinical investigator sites will remain open to trial participants for required in-person assessments or whether the clinical investigator has the ability to provide required in-person assessments at an acceptable alternate location(s), or whether such protocol-specified, in-person assessments can instead be conducted virtually.

• Assessing the continued availability of clinical trial supplies and continued operations of vendors, especially related to supply of the investigational product and/or to clinical trial supplies that are essential to maintaining appropriate safety monitoring or other key trial procedures.

This should include consideration of product stability (shelf life) if the treatment schedule is revised ...." (ibid).

IRBs and Review of Studies When New Sites Are Added to Project

The federal Office for Human Research Protections (OHRP) has issued a new guidance for IRBs and others involved in multisite experiments involving human subjects. This new guidance helps to interpret how to implement changes set in place by the revised Common Rule.

"On November 12, 2020, OHRP issued 'OHRP Guidance on Maintaining Consistency Regarding the Applicability of the 2018 or Pre-2018 Requirements: Options for How New Sites Added to Ongoing Cooperative Research Can Follow the Same Version of the Common Rule.'

The guidance responds to questions from the regulated community on how institutions can maintain consistency in the version of the Common Rule that applies to a cooperative research project in situations where an Institutional Review Board (IRB) approved the study at one or more sites before the general compliance date of the 2018 Requirements (i.e., the revised Common Rule), and other sites are added after the general compliance date of the 2018 Requirements" (on the Web at https://www.hhs.gov/ohrp/maintaining-consistency-regarding-2018-and-pre-2018-requirements.html).

IRBs Now Have Different Options For Compliance With Requirements

"In response to these questions, OHRP is clarifying the options with regard to whether the pre-2018 requirements or 2018 Requirements apply to institutions added as new sites for ongoing cooperative research.

This document describes permissible options, under 45 CFR §46.101(l), in cooperative research projects for which:

(1) the research was initially approved by an Institutional Review Board (IRB) for at least one study site prior to January 21, 2019 (the general compliance date of the 2018 Requirements); and

(2) at least one new site is added to the research on or after January 21, 2019.

If the two above two criteria are met, the following options are permissible:

• The pre-2018 Requirements can apply to the cooperative research at any subsequently added site, without further action by any institution involved in the research. 45 CFR §46.101(l)(3).

If the initial study sites are conducting the research under the pre-2018 Requirements, this approach will allow all institutions involved in the cooperative research to conduct the research under the pre-2018 Requirements" (ibid).

IRB Decision Can Apply to One Research Site Only

"• Any subsequently added site that prefers to conduct the cooperative research under the 2018 Requirements instead may transition the study at that site. 45 CFR §46.101(l)(3), (4).

(For more information about transition, see https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-revised-common-rule-compliance-dates-transition-provision-45-cfr-46-1011/index.html.)

Transitioned studies must comply with the single IRB review provision at §46.114(b)(1), unless an exception applies. See 45 FR §46.114(b)(2)(i) and (ii).

• If the initial study sites are conducting the research under the 2018 Requirements (e.g., because of a decision at those sites to transition the study conducted at those sites to the 2018 Requirements), this approach will allow all institutions involved in the cooperative research to conduct the research under the 2018 Requirements.

(Note that a site's decision to transition a study is limited to the conduct of the study at that institution, and at no other site.)

Please note that these are not the only possible approaches to how the 2018 Requirements at 45 CFR §46.101(l) can allow all sites in a cooperative research project to follow the same version of the Common Rule.

If regulated entities would like to discuss other possible approaches, please feel free to contact OHRP staff at OHRP@HHS.gov" (ibid). ©

IRBs and Research On Prisoners (#8)

We are nearing the end of this article series describing allegations of substantial violations of the regulations on the protection of human research subjects. One of the central accusations is that those responsible for the study with incarcerated prisoners didn't even get IRB approval of the alleged experiments.

Why? Because the company representatives who sold the involved drug to Louisiana, and the state government officials in charge, all claimed that the activity wasn't really research. Nationally reputable groups and individuals, including longtime experts on human subject protections, said otherwise.

As the complainant group known as Public Citizen wound up its arguments against the company BioCorRx and the Louisiana Department of Public Safety and Corrections (LDPSC), it added that there could be even more subject protection violations involved in the case.

Another Company "Pilot Program" Sounds Suspiciously Like Clinical Research

We resume where we left off last month with more excerpts from the section of the complaint to the FDA by Public Citizen's Dr. Michael Carome that is titled "Concerns about other possible clinical investigations conducted by BioCorRx."

> "We note that Mr. Granier [BioCorRx CEO] reportedly told The Advocate [Louisiana's largest newspaper, headquartered in Baton Rouge] that the sustained-release naltrexone implant had been 'used successfully by more than 1,000 people,'[11] suggesting the company has collected data on use of the implant in more than 1,000 subjects.
>
> [FN #11: Toohey G. Louisiana prisons pilot addiction-fighting implants for inmates; lack of FDA approval draws criticism. The Advocate. May 6, 2019. https://www.theadvocate.com/baton_rouge/news/crime_police/article_3376578e-6cfa-11e9-9442-1fea4f3f194a.html. Accessed November 12, 2019.]
>
> Moreover, BioCorRx previously has announced other pilot programs that used the sustained-release naltrexone implants that sound suspiciously like the apparent clinical investigation conducted by BioCorRx and the LDPSC in prison inmates, including the following:
>
> (1) On January 24, 2018, BioCorRx issued a press release announcing the launch of a 'paid demonstration pilot' for the BioCorRx Recovery Program in collaboration with the One Day At A Time Program (ODAAT), which is funded by the city of Philadelphia and the state of Pennsylvania.[12]
>
> [FN #12: BioCorRx. BioCorRx announces collaboration with the One Day at a Time Program in Philadelphia. January 24, 2018. https://ir.biocorrx.com/press-releases/detail/113/biocorrx-announces-collaboration-with-the-one-day-at-a-time. Accessed November 12, 2019.]" (Public Citizen complaint to FDA Commissioner Admiral Brett P. Giroir, M.D., November 20, 2019, p. 8 of 14; on the Web at https://www.citizen.org/wp-content/uploads/2499.pdf).

Other Program Goes "As Planned"

> "According to the press release, the ODAAT serves low-income and homeless men and women and their families in the Philadelphia area who are afflicted with addiction and HIV/AIDS -- individuals who, like prison inmates, would be highly vulnerable to coercion or undue influence.
>
> (2) On October 5, 2017, BioCorRx issued a press release announcing the start of a pilot program for weight loss in collaboration with the Atlantis Medical Wellness & Weight Loss Center in Silver Spring, MD ....
>
> The pilot program uses sustained-release naltrexone implants. Importantly, no FDA-approved naltrexone product is approved for weight reduction. On March 15, 2018, BioCorRx reported that twelve individuals had been successfully enrolled in the pilot program 'as planned' and that 'the initial results have been positive as reported by patients' " (supra at pp. 8-9). © {TBC}

IRBs and Parental Permission In Research With Children (#3)

With this article we conclude our coverage of the important set of recommendations on research with children that was issued by the Secretary's Committee on Human Research Protections (SACHRP). This guidance focuses on what "not reasonably available" means when seeking parental permission for a child's participation in research.

We resume here where we left off last by presenting the final segment from a portion of SACHRP's open letter to HHS that is titled "Attachment D -- Parental Permission in Research With Children," as follows.

"The term *reasonably available* should be applied both to (1) locating a parent and (2) the mechanism that can be used to secure that parent's permission.

For example, parents may be reasonably available because they have been located; however, there may be no reasonably available mechanism to obtain the second parent's signature on a permission form" (October 17, 2018; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-d-november-13-2018/indes.html, page 4). [sic]

When a Parent Is Not "Reasonably Available"

"**4. Application of 'Reasonably Available' to Locating a Parent**

Overall, if a parent's role in the care of and/or decision-making about the child, even if limited, is such that his or her involvement and location may be readily ascertained, the parent is considered reasonably available and attempts at contact should be pursued.

'Not reasonably available' is not intended to mean that a parent is temporarily unavailable, unless there are specific circumstances where time is of the essence.

There are numerous specific situations that could support a determination that a parent is not reasonably available. In general, however, a parent who is not reasonably available is one whose whereabouts are unknown; who should not be contacted because of the nature of the relationship between the parent and child; whom there is no way to reach by phone, mail, email, fax or any type of video-conferencing; or who has not responded to multiple contact attempts.

'Not reasonably available' does not apply to situations when a parent is at work, traveling, not immediately available by electronic means, or living in another state or country, without more to justify the investigator's inability to reach the parent and seek permission" (ibid).

Examples for IRBs and Researchers

"Examples of situations when one may reasonably conclude that a parent is not reasonably available could include the following situations:

- The parent is incarcerated and not contactable.
- The parent is on active military duty and not contactable.
- The parent's whereabouts are unknown.
- The parent is known and contactable but chooses not to be involved in the child's care.
- The parent is known but, upon inquiry, there is reason to believe that requesting permission would be inconsistent with the parent/child relationship, such as where there is reason to believe there is or has been domestic violence or other situations involving harm to the health or welfare of the child.

5. Application of 'Reasonably Available' to Documentation of Permission by a Parent

A determination that a parent is 'not reasonably available,' per the regulations, may include circumstances in which a parent is available to participate in the consent process and has given permission for the child's participation, but is not able to provide a valid signature.

A second parent's inability to provide a signature must not be used as a reason not to involve that parent in the consent process, or as a reason not to respect that parent's decision.

SACHRP recommends that OHRP and FDA produce joint guidance that describes types of documentation that would satisfy the requirements of 45 CFR 46.117/21 CFR 50.27 in addition to the traditional mechanism of physically signing a document" (supra at pp. 4-5). ©

IRBs, Research, and Public Surveillance (#1)

We introduce here a new set of recommendations for IRBs and others from the Secretary's Advisory Committee on Human Research Protections (SACHRP). This set focuses on a relatively unusual topic for IRBs in a document titled "Attachment A -- Public Health Authority and Surveillance Activities: Interpretation of Public Health Authority and Public Health Surveillance Activities, 45 CFR Part 46.102(k), 46.102(l)(2)."

A major question inherent in this document can be paraphrased as "Is it human research or not and, if so, which federal regulations apply?" The impetus behind this new set of recommendations is the fact that the paraphrased topic above is one being posed now by IRBs across the U.S. to the federal Office for Human Research Protections (OHRP).

In turn, one of the reasons such a question is being posed is the COVID-19 pandemic. Although the particular human subjects issue involved has been relevant enough to have been discussed when the Common Rule was revised, the heightened amount of public scrutiny over the pandemic now has led to even more confusion in the research compliance community.

New Human Subject Regulations Coming?

The need for the new advice from SACHRP is explicitly acknowledged in the document itself, as OHRP states that:

> "OHRP is frequently asked to respond to questions from the research community regarding the interpretation and application of 45 CFR part 46.102(k) and (l)(2). While OHRP and other HHS agencies have already considered these questions, OHRP asks SACHRP to independently deliberate the questions below and come to its own objective recommendations.
>
> OHRP would be interested in SACHRP's views even if additional rulemaking were necessary to clarify or modify aspects of the regulations.

The regulatory text is as follows:

> **45 CFR part 46.102(k)**
>
> Public health authority means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate" (SACHRP, Attachment A to letter from SACHRP to Alex Azar, Secretary of the Department of Health and Human Services, October 26, 2020, p. 1 of 27; on the Web at https ://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-public-health-authority-and-surveillance-activities/index.html).

"Surveillance Activity" Has Wide Scope

> **"45 CFR part 46.102(l)(2)**
>
> Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
>
> Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products).
>
> Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

In the pre-2018 version of the Common Rule, there were a number of categories of exempt research which were presented at 45 CFR part 46.101(b)(1) through (b)(6). Of note, these are human subjects research, but research that is exempt from the requirements of the Common Rule.

In the revised Common Rule, known as the 2018 Requirements, those exemptions were modified extensively and were moved to 45 CFR part 46.104" (supra at p. 2). © {TBC}

IRBs, Drug Interaction Studies, And Human Subject Safety

We introduce here a particular type of drug interaction study that contains useful information for IRBs. We will highlight those portions on subject safety and IRB issues that are most salient.

However, since most of the cited FDA guidance is specific for this type of research, we refer interested readers to the rest of the guidance for its other recommendations.

The guidance in question is titled "Clinical Drug Interaction Studies With Combined Oral Contraceptives" (on the Web at https://www.fda.gov/media/143849/download).

> "This guidance assists sponsors of investigational new drug applications and new drug applications in evaluating the need for and design [of] drug-drug interaction (DDI) studies involving combined oral contraceptives (COCs) during drug development as well as determining how to communicate the results and recommendations from the DDI studies" (85 Fed. Reg. 74737, November 23, 2020).

What to Do If Abnormality Is Possible

> "COCs contain two synthetic steroid hormones, a progestin and an estrogen. COCs are highly effective in preventing pregnancy when used correctly.
>
> However, drug interactions with concomitant therapies can adversely impact the efficacy and/or safety of COCs by affecting enzymes involved in the metabolism of progestins and estrogens.
>
> For example, decreased progestin concentrations can lead to unintended pregnancy (loss of efficacy), whereas increased estrogen and/or progestin concentrations can increase the risk of venous thromboembolisms (VTEs), a rare but serious adverse event.
>
> Because COCs are widely used in women of childbearing potential, and many investigational drugs are co-prescribed with COC after approval, clinically relevant DDIs between an investigational drug and COCs should be: (1) evaluated during drug development of the investigational drug; (2) understood via *in vitro* and/or clinical assessment at the time of the investigational drug's approval; and (3) communicated in the labeling, as needed" (guidance, November, 2020, p. 2).

There are specific dangers for research subjects described in the guidance. For example:

> "If the investigational drug has teratogenic [i.e., can cause an abnormality] potential,[5] then regardless of the *in vitro* or *in vivo* DDI study results, a COC DDI study should be conducted, unless an *in vivo* DDI study using a CYP3A [Cytochrome P450 3A] probe substrate has already shown that the investigational drug is a moderate or strong CYP3A inducer, in which case the labeling should recommend avoiding concomitant use with COCs ....
>
> [FN #5: Ahn MR, L Li, J Shon, ED Bashaw, and M-J Kim, 2016, Teratogenic Drugs and Their Drug Interactions with Hormonal Contraceptives, Clin Pharmcol Ther, 100: 217-219.]" (supra at p. 4).

Some Study Designs Are Better Than Others

As for most FDA guidances with warnings about research design and potential effects on subject safety, this guidance has specific recommendations about the choice of study population. For example:

> "• Either premenopausal or postmenopausal women can be included in the DDI study; however, including premenopausal females allows for the assessment of pharmacodynamic (PD) endpoints that cannot be studied in postmenopausal subjects.
>
> • The number of subjects included in a COC DDI study should be sufficient to provide a reliable estimate of the magnitude and variability of the interaction" (supra at p. 4).

The guidance also contains other recommendations on study design and types of drug sampling to be conducted to minimize risks. For example:

> "• Fixed sequencer or randomized crossover studies are preferred. If these designs are not feasible, a parallel study design is acceptable ...." (supra at p. 5).

FDA is accepting comments on the new guidance ***until February 22***. For more information, contact: Lauren Milligan of the Center for Drug Evaluation and Research at 301-796-5008, or send email to OCP@fda.hhs.gov. ©

OHRP Investigation

Project Title: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Trial - ***Article #2***
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.

* * *

Alleged Violations of Ethical Principles and Federal Regulations on Human Subjects

It has become increasingly clear that this OHRP investigation, initiated by complaints from the consumer advocacy group known as Public Citizen, warrants far more attention in the HRR.

We first described some potential violations of human subject protection regulations in our June and July 2019 HRRs. Last month, in our lead article, we began to add more detailed information.

Follow-up charges by Public Citizen in late 2020, and a formal response by OHRP, has made it clear that numerous problems appear to be associated with the relevant research. Even more troublesome is the number of prestigious academic medical centers and related U.S. institutions involved.

Hence, we have assembled a number of reports for a chronological study of the IRB-related events and the applicable important lessons for other IRBs inherent in this chain of developments.

We begin with a recent summary statement from OHRP on just what the involved research entails. We shall immediately follow that statement with Public Citizen's rejoinder characterization of the same study's risks to human subjects and what has, and has not, been done to minimize those risks.

> "CLOVERS is a multicenter, randomized un-blinded, two-arm clinical trial to determine the impact of a restrictive fluids ('Medicine to Raise Blood Pressure First') strategy as compared with a liberal fluids ('Fluids First') strategy on 90-day in-hospital mortality.
>
> It is funded by the National Heart, Lung[,] and Blood Institute (NHLBI) and led by emergency medicine and critical care medicine experts from the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network.
>
> The PETAL Network is a network of twelve clinical centers and one clinical coordinating center competitively funded by the NHLBI after peer review to develop and conduct randomized controlled clinical trials to prevent Acute Respiratory Distress Syndrome (ARDS) or provide early treatment to improve the outcome of patients who have ARDS" (letter from OHRP's Lisa Buchanan, Director of Compliance Oversight, to Dr. Michael Carome, Director of Public Citizen's Health Research Group, September 20, 2020, p. 3 of 7; on the Web at https://www.citizen.org/wp-content/uploads/CLOVERS-OHRP-response-to-Public-Citizen-Final-9.28.2020.pdf?eType=EmailBlastContent&eId=ceea547b-c389-4182-8d2c-b6a2d9cccd03).

Alleged Risks to Subjects Include Death

With this central background picture presented, we now begin our chronological coverage of the CLOVERS controversy. We refer readers to our July 2019 HRR for a preliminary summary of the serious faults found by Public Citizen in the design of the study, including an allegedly misleading informed consent form and a dangerously flawed overall study design.

> "The misalignments in CLOVERS are so outside the norms of treatment that it is obvious they carry an unacceptable increased risk of organ failure and death and should be avoided, but the trial's design compels such risky deviations from usual care in many septic subjects ....
>
> In addition, the IRB-approved sample consent form fails to comply with key provisions of HHS regulations at 45 C.F.R. §46.116(a)" (letter from Public Citizen's Drs. Michael Carome (Director, Health Research Group and a former OHRP official) and Sidney Wolfe (Founder and Senior Analyst), to Jerry Menikoff, M.D., J.D. (OHRP Director), August 28, 2018, p. 2; on the Web at https://www.citizen.org/sites/default/files/2446.pdf). © **{TBC}**

FDA Warning

Warning Letter To: Houston, TX IRB (Part 3)
Warning Letter Date: September 24, 2012
Investigation Period: Ended on April 25, 2012
Noncompliance: IRB Members Repeatedly Failed to Follow Regulations

* * *

FDA Refuses to Accept IRB's "Explanation"

We continue here with this unusually instructive FDA investigation that produced, at first, Warning Letters to a Texas IRB, and then finally to its FDA-ordered complete dissolution. In resuming where we last left off, we present finding #4 from the investigation's first Warning Letter, as follows:

"4. The IRB failed to determine that a pediatric study is in compliance with Part 50 Subpart D ((21 CFR §§ 56.109(h) and 56.111(c)).

Under 21 CFR Part 50 Subpart D, Additional Safeguards for Children in Clinical Investigations, IRBs are required to review clinical investigations involving children as subjects covered by Subpart D and approve only those clinical investigations that satisfy the criteria within certain risk categories identified in sections 50.51, 50.52, or 50.53 under Subpart D.

A. The meeting minutes from January 8, 2012, show that the IRB reviewed and approved an investigational ...[redacted by FDA] study involving children. The meeting minutes do not document the IRB's determination of the level of risk involved, the potential for direct benefit, the likelihood of yielding generalizable knowledge about the subjects' disorder or condition, and the opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

B. The meeting minutes from January 8, 2012, do not document that the IRB discussed and/or determined adequate provisions were made for soliciting the assent of the children involved in the investigational ... [redacted by FDA] study.

In your letter you state that all future studies involving pediatric subjects will be more closely scrutinized. Also in your letter you reference an FDA Guidance for IRBs and Clinical Investigators -- Informed Consent Document Content which provides that FDA does not require the informed consent document to contain a space for assent by children.

We do not accept your explanation. The observation on the Form FDA 483 does not speak to whether FDA requires the Informed Consent document to contain a space for assent by children.

Instead, the FDA investigator observed that the IRB failed to determine at the time of the initial review that the research study was in compliance with 21 CFR Part 50 Subpart D" (initial FDA Warning Letter, pp. 2-3).

IRB Will "Recreate" Destroyed Documents

"Additionally, please note that 21 CFR Part 50, Subpart D requires IRBs to find and then document that the clinical investigations involving children as subjects meets the requirements of Subpart D. The meeting minutes for January 8, 2012, fail to document additional requirements for review of this study involving pediatric subjects.

5. The IRB failed to prepare and maintain adequate documentation of IRB activities. (21 CFR §56.115).

A. The IRB did not maintain meeting minutes for 2011. During the inspection you told the FDA investigator the IRB met twice in 2011. According to your study list, protocol ... [redacted by FDA] was modified and approved on August 24, 2011, but no meeting minutes were available for review documenting the IRB's activities.

In your letter, you confirm that there are no meeting minutes for 2011 during which two meetings were held. You explain that due to a computer crash all minutes and data for that time frame were lost. You stated that you would 're-create' the meeting minutes and provide them at a later date.

It is inappropriate and an unacceptable record keeping practice for the IRB to re-create minutes for 2011. In your response to this letter, please provide proposed corrective actions to prevent future occurrence of the loss of required records" (supra at pp. 3-4). © **{TBC}**

In Court

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 45)
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

* * *

Plaintiff Says Students Had No Choice At All

The next development in this case came as a "Statement of Facts" by the former research subject who was a female high school student-athlete. At this point in the lawsuit, amidst the charges and counter charges, the actual facts had become rather buried.

Therefore, we present this section of the court document cited below as a reminder of what the case really involved. However, we also note that these "facts" are presented by the plaintiff, not by a impartial third party.

"II. Statement of Facts

In 2000, the [school] Districts [in Oregon] agreed to participate in an experiment known as SATURN, a three (3) year federal health study (the 'experiment') being funded with a $3.6 million grant from the National Institutes of Health and the National Institute of Drug Addiction ....

The experiment was administered through OHSU .... The purpose of the experiment was to determine if drug testing reduces drug use among all students .... As part of the experiment, the District instituted mandatory drug testing for every student-athlete ....

All high school students who desired to participate in sports had to submit to a random urinalysis drug test and to sign a consent form that ostensibly permits SATURN researchers full access to the drug test results ....

If a student refused to sign the consent form or to participate in the drug test, he or she would not receive a drug test and would be prohibited from playing any sports at his or her high school .... The consent forms themselves were misleading and inconsistent ...." ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, p. 3).

Blatant Coercion Is Alleged By Plaintiff

"The experiment's protocol counts a test subject's refusal to provide a urine sample as a positive drug test result .... Also, as part of the experiment, students were forced to answer intrusive questionnaires related to drug use ....

If students questioned the legality of the experiment or refused to participate in the drug testing or to answer the questionnaires, they became the subject of personal attacks by the defendants or agents of the defendants ....

In 2002, Wade [the plaintiff] was forced to participate in the experiment in order to play sports .... In October 2002, after the Complaint was filed, OHRP [federal Office for Human Research Protections] suspended the SATURN experiment and made the following findings, among others:

1. Mandatory drug testing is an integral part of the design of the SATURN research protocol. The goals of the mandatory drug testing of student athletes and the scientific aims of the study are so closely interwoven as to be indistinguishable.

Most, if not all, of the schools participating in the SATURN study had no drug testing policies prior to being approached by investigators. Several schools had not even considered drug testing athletes until approached by the SATURN investigators. The SATURN project pays for the drug testing.

2. The circumstances under which subjects were enrolled was done without minimizing the possibility of coercion or undue influence and failed to obtain informed consent from the subjects. The threat of being disqualified from athletics if a student did not participate in the research was coercive" (supra at pp. 3-4). © {TBC}

Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** Comments are being accepted by the agency on a final guidance titled "Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment."

This guidance contains ***useful recommendations for IRBs and researchers***, including ***study design and human subject population enrollment advice***. These recommendations could affect how to interpret study results and, in turn, ***impact an IRB's assessment*** of whether or not the benefit-risk ratio is justifiable for involved research subjects.

The announcement of this guidance occurred on October 2, 2020, in the FEDERAL REGISTER (85 Fed. Reg. 62305). The guidance itself is on the Web at https://www.fda.gov/media/114948. For more information, contact: Silvana Borges of FDA's Center for Drug Evaluation and Research at 301-796-0963.

• **Food and Drug Administration.** Comments are being accepted ***until March 1*** on a draft guidance titled "Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents [ARAs]: Study Design, Data Analysis, and Clinical Implications." This guidance contains ***information of immediate use for IRBs that review relevant studies,*** given possible ***risks for human subjects*** and the ready access to OTC ARAs for most people.

> "Because ARAs can elevate the gastric pH, concomitant administration of a drug with an ARA could alter the solubility, dis solution, and bioavailability of the drug, potentially resulting in a ***loss of efficacy*** for weak-base drugs or ***increased toxicity*** for weak-acid drugs.
>
> Therefore, it is important to assess the susceptibility of an investigational drug to gastric pH change-mediated DDIs [drug-drug interactions] ***early in drug development*** ...." (85 Fed. Reg. 77222, December 1, 2020).

The guidance itself is on the Web at https://www.fda.gov/media/144026/download. For more information, contact: FDA's Anuradha Ramamoorthy at the Center for Drug Evaluation and Research at 240-402-6426.

• **National Institutes of Health.** NIH has issued its own ***requirements for IRBs*** and institutions when multisite studies are involved.

The NIH announcement is an agency-specific interpretation of the recent broader scope notice by the federal Office for Human Research Protections (OHRP) on the same topic (see our November 2020 HRR lead article for details).

> "For as long as the OHRP's determination is in place, ***NIH will not require use of a single IRB for NIH-funded research*** that qualifies for an exception as outlined in the OHRP COVID-19 Exception Determination ***and for which the use of the exception is approved by NIH***.
>
> Approved exceptions apply for the duration of the NIH-conducted or supported research .... ***To request an exception to use of a single IRB***, eligible applicants, offerors, or recipients for NIH-conducted or supported cooperative research ***must submit an exception request to NIH***, including justification as to why the study meets the exception criteria defined by OHRP ....
>
> Applicants who wish to seek an exception must provide the exception request and accompanying justification in the Other Attachments section of the Research & Other Related Project Information form in the grant application ...." ("Exceptions to Use of a Single IRB During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency," Notice No. NOT-OD-21-006, October 23, 2020; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-006.html).

For more information, contact: NIH Office of Extramural Research via email to SingleIRBPolicy@mail.nih.gov.

• **Secretary's Advisory Committee on Human Research Protections.** According to OHRP, the SACHRP is seeking candidates for appointment to the SACHRP. Nominations will be accepted ***until February 12***.

OHRP cautions that federal employees should ***not*** be nominated for appointment to the committee (excerpted from an email by OHRP, December 14, 2020).

For more information, OHRP recommends the following Web page: https://www.govinfo.gov/content/pkg/FR-2020-12-14/pdf/2020-27417.pdf (this is a FEDERAL REGISTER page). ©

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.

• **January 26-28, 2021**, virtual workshop: **"Clinical Site Coordinator/Manager and GCP Workshop."** Topics include: informed consent and how to submit a protocol to an IRB. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org.

• **March 17-18, 2021**, in Newport Beach, California: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP."** The topics will include: informed consent; how FDA performs inspections of clinical investigators; the ethics of clinical research related to patient treatment; the duties and responsibilities of Institutional Review Boards (IRBs); and informed consent requirements. Contact: Conference Registrar, SoCRA, at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **April 15-16, 2021**, in Portland, Oregon: **"Clinical Site Coordinator/Manager and GCP Workshop."** Topics include: informed consent and how to submit a protocol to an IRB. 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 22-23, 2021**, in New Orleans, Louisiana: **"Hot Topics and Practical Considerations for Protecting Human Research Participants."** Topics 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, regulatory compliance, etc. Contact: MAGI's Norman Goldfarb at 650-465-0119.

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