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PROTECTING RESEARCHERS AND RESEARCH SUBJECTS

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IRBs and Assessment of Benefit-Risk Ratios (#1)

Traditionally, the assessment of benefit-risk ratios for human subject study participation has been at the heart of IRB reviews of research protocols.

A recent draft FDA guidance addresses numerous aspects of such judgments, emphasizing benefit-risk evaluations in the development of new drugs and biological products.

The guidance is titled "Benefit-Risk Assessment for New Drug and Biological Products." We find this guidance to be of particular interest because it includes a focus on an increasing phenomenon in clinical trials; namely, the use of human subject self-reports by IRBs and researchers in evaluating study results and the resultant justification of experimental designs.

As we have reported recently, the increasing predominance of using "PROs" (patient reported outcomes) in evaluating research results is posing special challenges for IRBs.

Hence, this new guidance may prove especially useful to IRBs involved in reviewing drug and biologics experiments.

Use of Subject/Patient Experience in Making Benefit-Risk Assessments

"This guidance articulates important considerations that factor into the Center for Drug Evaluation and Research and the Center for Biologic's Evaluation and Research's benefit-risk assessments for drug products, including how patient experience data may be used to inform benefit-risk assessment.

It discusses how sponsors can inform FDA's benefit-risk assessment through the design and conduct of the development program, as well as how they may present benefit and risk information in the marketing application ….

The guidance concludes with additional considerations on benefit-risk assessments that inform regulatory decision making that occurs in the postmarket setting" (86 Fed. Reg. 54212, September 30, 2021).

For IRBs reviewing studies that may lead to researcher submissions to FDA, understanding the agency's views on benefit-risk analyses can be quite useful.

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 or edit text/formating in brackets [ ] to make the material easier to read, or to add an underline emphasis.

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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Therefore, we present below the guidance's discussion of factors that IRBs may have to weigh as well.

"B. The Impact of Uncertainty on Benefit-Risk Assessment

FDA's benefit-risk assessment carefully considers the strength and quality of the evidence available and takes remaining uncertainties into account in every dimension of the Benefit-Risk Framework" (guidance, September, 2021, p. 10 of 20; on the Web at https://www.fda.gov/media/152544/download).

"Uncertainties" and Their Impact Upon Benefit-Risk Assessments

"Uncertainties that can affect benefit-risk assessments may include, but are not limited to:

- Limits on scientific understanding of the patient population and natural history of the condition, e.g., due to heterogeneity of disease manifestations and progression in the patient population, or lack of identification of risk factors or prognostic biomarkers.
- Aspects of the program or study design, such as the population, choice of controls, endpoints, duration, and data sources, as well as any differences between the clinical study and real-world use.
- Reliability of the estimates of benefit or risk, based upon variability in estimated effects due to sampling (statistical uncertainty) or issues with trial conduct such as missing data, poor protocol compliance, etc.
- Limited understanding of the effects of the drug that may be used in combination with existing therapies (e.g., potential beneficial adjunctive effect, potential for adverse drug-drug interactions, etc.).
- Proposed risk management strategies, such as patient monitoring, which have not been studied in clinical trials, or that have been studied in clinical trials but would be potentially difficult to implement in practice.
- Limited patient input on disease burden and unmet medical needs, meaningfulness of potential benefits, and acceptability of risk tradeoffs and uncertainty …." (ibid).

Accepting Some Uncertainty

"Many sources of uncertainty can be anticipated and potentially avoided with careful attention to trial design during product development stages, as discussed further in section IV. At other times, uncertainties become apparent only after the trial evidence has been generated, such as the appearance of an unexpected safety signal ....

Therapeutic context plays an important role in FDA's assessment of the acceptability of uncertainty. For a drug intended to treat a serious disease with unmet needs, FDA may accept greater uncertainties about benefit or risk at the time of approval, for example through the accelerated approval pathway[22].

[FN #22: For more information about accelerated approval, see FDA's guidance for industry *Expedited Programs for Serious Conditions -- Drugs and Biologics* (May 2014), available at the FDA guidance web page.]

A higher degree of uncertainty is common in drug development programs for rare diseases, where the prevalence of disease, and consequent limitations of study size, can limit the precision of safety and efficacy characterizations.

FDA recognizes that when a drug is developed to treat serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable provided that the substantial evidence standard has been met.

FDA therefore often exercises greater regulatory flexibility in these cases, in particular by accepting clinical trials that have lower sample sizes" (supra at pp. 10-11). © {TBC}

IRBs and FDA's Advice on How To Cope With Coronavirus (#7)

We continue here with more recent updates for IRBs and others on the effects of COVID-19 on different types of human subjects studies.

Our focus in this article is on the revised Q&A 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."

We resume where we left off in the December, 2021, HRR with the FDA's advice for IRBs and others on whether to halt or to continue certain types of human subjects research during the COVID crisis.

> "Pausing enrollment in a trial to decrease potential exposure to COVID-19 would not generally be expected to significantly affect trial participant safety, the scope of the investigation, or the scientific quality of the study; therefore, submitting a protocol amendment would not be required under the regulation for such a pause" (guidance, rev. December 4, 2020, p. 10 of 35; on the Web at https://www.fda.gov/media/136238/download).

Role of IRBs During Pandemic

> "Protocol amendments that are not required to prevent imminent safety risks to patients can be implemented after they are submitted to FDA and IRB approval has occurred ....
>
> FDA recognizes that during the rapidly evolving circumstances of the current COVID-19 public health emergency, a sequence of changes may be needed to address those circumstances.
>
> Clinical investigators must document as protocol deviations any modifications to protocol-specified procedures that occur prior to IRB approval and submission of the protocol amendment implementing the modification ....
>
> Consolidating several protocol modifications in a single protocol amendment would be acceptable but should be submitted expeditiously.
>
> For studies under an IDE, 21 CFR 812.35 (a) generally requires prior FDA approval before implementing changes to the investigational plan.
>
> These requirements do not apply to changes made to protect the life or physical well-being of a trial participant in an emergency, including study-wide changes, but such deviations must be reported to FDA within 5 working days ...." (supra at p. 10).

Key Role of IRBs Remains Unchanged

> "In addition, under 21 CFR 812.35(a)(3), changes to the protocol that the sponsor determines, based on credible information, do not affect the validity of the results from the study, the likely patient risk-to-benefit relationship, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the trial participants may be made without prior FDA approval, if the sponsor reports the modifications to the agency within 5 days of implementing the changes.
>
> Because of the unique and evolving circumstances surrounding the impact of COVID-19, we understand that it may be challenging to submit 5-day reports/notices within the required timeframe.
>
> Sponsors may consolidate implemented changes when submitting 5-day reports/notices and should update the IDE as soon as possible.
>
> **Q4. How should a sponsor submit a change in protocol that results from challenges related to the COVID-19 public health emergency?**
>
> For IND studies, the sponsor should submit a formal amendment to its IND, with the following information added to the cover letter in the subject line:
>
> *Protocol Amendment -- COVID-19*
> *Title of Protocol*
>
> Sponsors should summarize the major changes made to the protocol related to COVID-19 in the cover letter and should include a tracked changes version of the protocol to facilitate review.
>
> As with other protocol amendments, sponsors may implement protocol amendments due to COVID-19 upon submission to FDA if approved by the IRB. Sponsors seeking FDA input prior to implementation should indicate that in the cover letter" (supra at p. 11). © {TBC}

IRBs, Cancer, and Patients With CNS Metastases (#2)

As we introduced in the August, 2021, HRR, a certain type of study poses special problems for IRB protocol reviews. This is especially true for IRB analyses of study design factors in relevant cancer experiments, including whether the benefit-risk ratio for human subjects is justifiable.

The recent FDA guidance that applies to these situations is titled "Evaluating Cancer Drugs in Patients with Central Nervous System [CNS] Metastases." Although the main focus of the guidance is on the science, we have selected portions that can affect IRB reviews.

> "Study design challenges for CNS metastases include uncertainty regarding optimal endpoints, lack of standardized response assessments, understanding how CNS metastases are evaluated in the context of the entire burden of metastatic disease to characterize a drug's potential benefit (e.g., timing of CNS radiographic assessments relative to other sites of metastases), and interpreting radiographic response in the setting of recent radiation therapy or surgery" (86 Fed. Reg. 35307, July 2, 2021).

Trial Design Considerations As Crucial IRB Review Topics

Our primary interest in this FDA guidance lies with Section III ("Clinical Trial Design Consideration") since that is an area of interest for IRBs. For example,

> "The recommendations discussed below pertain to clinical trials for systemic anticancer drugs where patients with CNS metastases are included in the study population …. These recommendations are also applicable to trials conducted exclusively in patients with CNS metastases.
>
> **A. Patient Population**
>
> FDA recognizes that treatment of CNS metastases presents several challenges and unique considerations (e.g., circumventing the blood-brain barrier); however, CNS disease should not be evaluated in isolation from metastatic disease in the rest of the body.
>
> FDA will evaluate effects of systemic drugs on CNS metastases in the context of the entire burden of metastatic disease, regardless of whether the trial was conducted exclusively in patients with CNS metastases or in a population where only a subset of patients has CNS metastases" (guidance, July, 2021, p. 2; on the Web at https://www.fda.gov/media/141507/download).

Taking Into Account Any Previous Treatments

> "Therefore, efficacy claims based on endpoints measuring CNS activity alone may not be appropriate. For example, evaluation of the clinical significance of overall response rates (ORR) or progression-free survival (PPS) that considers only CNS disease sites (CNS-ORR or CNS-PFS, respectively) is difficult to interpret as it does not take into account extra-CNS metastatic disease ….
>
> **B. Available Therapy**
>
> For the purposes of determining whether an expedited program is an appropriate regulatory pathway for a given drug, an available therapy for a metastatic solid tumor would be an available therapy[5] for CNS metastases of that solid tumor, unless otherwise specified in the labeling for that therapy (e.g., the drug is contraindicated for CNS metastases) ….
>
> [FN #5: For the definition of available therapy, see section III.B of the guidance for industry *Expedited Programs for Serious Conditions -- Drugs and Biologics* (May 2014).]
>
> Showing comparability to available therapy for treatment of overall metastases and demonstrating superiority for treatment of CNS metastases activity may be sufficient for expedited review considerations of a given drug.
>
> **C. Prior Therapies**
>
> FDA recommends that trial designs incorporate the following elements regarding therapies that subjects may have received prior to enrolling in the trial:
>
> • Case report forms should be designed to capture information on all prior CNS-directed treatments such as surgery, stereotactic radiosurgery (SRS), or whole brain radiation therapy (WBRT), including the dates of such therapy and response to therapy at baseline" (supra at pp. 2-3). © {TBC}

IRB Is Alleged to Have Violated Regulations (#1)

Allegations have been made that a Minnesota IRB approved controversial experiments with human subjects and thereby violated federal regulations on the protection of human subjects.

The allegations were levied recently against the Hennepin County Medical Center (HCMC) by the national consumer advocacy group known as Public Citizen (PC).

> "'The U.S. Food and Drug Administration (FDA) should promptly initiate serious enforcement proceedings -- specifically, a formal process called disqualification -- against two researchers at … [HCMC] in Minneapolis, Minn. who repeatedly and deliberately violated agency regulations intended to protect human subjects' Public Citizen said today in a petition to the agency" ("FDA Must Promptly Punish Researchers at Minnesota Hospital Who Conducted Unethical High-Risk Experiments, Require Patients Be Informed Their Rights Were Violated," November 17, 2021; on the Web at https://www.citizen.org/news/fda-must-promptly-punish-researchers-at-minnesota-hospital-who-conducted-unethical-high-risk-experiments-require-patients-be-informed-their-rights-were-violated/).

IRB Should Be Punished Too, Says Group

> "The doctors conducted a series of clinical trials that tested the dangerous general anesthetic ketamine and powerful sedatives on agitated patients without their consent.
>
> The consumer watchdog group [i.e., PC] also asked the FDA to take similar harsh action against the HCMC Institutional Review Board (IRB) for violating federal human subjects protection regulations by approving these trials without ensuring that informed consent requirements for such experiments were implemented.
>
> 'The pattern of repetitive egregious violations by the HCMC researchers and IRB … demand the most serious punishment to hold those responsible accountable ...' said Dr. Michael Carome, director of Public Citizen's Health Research Group" (ibid). © **{TBC}**

IRBs and Core PROs in Cancer Clinical Trials (#4)

We continue in this article with more coverage of experimental design features from an FDA guidance on cancer research that we last presented in our December, 2021, HRR. The guidance is titled "Core Patient-Reported Outcomes [PROs] in Cancer Clinical Trials" (86 Fed. Reg. 30944, June 10, 2021).

We present more of this guidance's advice, especially for IRBs, because PROs pose special challenges for IRBs, due to the obviously subjective nature of PROs.

The guidance contains practical advice for IRBs for reviewing trial design aspects to ensure sufficient research validity to justify human subject participation. For example:

> "The following should be considered when determining the frequency of PRO assessment for core PROs:
>
> • A baseline assessment(s) should be included as a reference point for assessing change" (guidance, June, 2021, p. 6; on the Web at https://www.fda.gov/media/149994/download).

How Often Should PROs Be Assessed?

> "• Assessment frequency should be higher within the first few treatment cycles and depending on the trial may be less frequent in later cycles.
>
> • Assessment frequency should take into account the administration schedule of the drug(s) under study.
>
> • Different assessment frequencies can be selected for each core concept depending on the outcome and research objective.
>
> A standard approach to assessment frequency over the first year of therapy would aid in consistency and interpretation across advanced cancer trials …. How a therapy is administered can affect the timing of assessments.
>
> For example, intermittently administered intravenous (IV) cytotoxic chemotherapy often has the maximum intensity of symptomatic AEs earlier in each cycle, whereas this may not be the case with an oral drug administered on a continuous daily schedule" (supra at pp. 6-7). © **{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 A - Addressing Ethical Concerns, Offers of Payment to Research Participants" - *HRR Article #12*
Document Source: Attachment, Letter to Alex Azar, Secretary, Department of Health and Human Services
Document Date: November 30, 2019
Available At: https://www.hhs.gov/ohrp/September-30-2019-letter-hhs-secretary.html

* * *

When to Pay Human Research Subjects

With this article we conclude our presentation of the highlights of the SACHRP document cited above, and begin coverage of a subsequent related set of SACHRP recommendations for IRBs and researchers. Although the first document discusses payments to research subjects, the next one deals with a very different topic; namely, charging subjects for their participation.

We begin by presenting the conclusion of the SACHRP set of recommendations on paying and/or reimbursing human research subjects.

"Advertising payment

10. SACHRP recommends that OHRP and FDA guidance acknowledge the permissibility of advertising study payment.

Payment of any type is intended to facilitate enrollment, which it cannot do if participants are not made aware of the offer. If an IRB has approved payment, there is no reason it should be treated as a secret or surprise; advertising payment may motivate individuals to enroll on that basis, but if the payment is acceptable, so is that motivation.

Because advertising is the first step in the consent process, payment information on advertisements should be truthful, clear, and appropriately contextualized with regard to study risks and burdens. This means that the availability and amount(s) of payment should not be highlighted to a greater extent than other relevant information about a study or in a way that obscures such information. However, it also need not be excluded from advertising materials.

Conclusion

The 2018 FDA revised guidance regarding participant payment is a step forward in its explicit recognition that reimbursement payments do not raise concerns about undue influence.

However, as articulated in this document, SACHRP believes that this guidance does not go far enough in easing concerns about offers of payments to research participants.

For the reasons stated above, SACHRP recommends that FDA and OHRP issue guidance that recognizes that, in addition to reimbursement payments, compensation and token appreciation payments do not raise concerns about undue influence.

SACHRP further recommends that FDA and OHRP issue guidance that recognizes [that] the concerns about unduly influential incentive payments can be managed without necessarily lowering or eliminating the payments, and outlines ways to minimize the possibility of undue influence.

SACHRP believes such guidance could support IRB decision-making regarding participant payments and encourage appropriate use of payments to facilitate the conduct and completion of research" ("Addressing Ethical Concerns …," p. 12 of 13).

Circumstances for Charging Subjects

The subsequent set of IRB recommendations from SACHRP is titled "Attachment A -- Charging Subjects for Clinical Trial Participation." As the title makes clear, this SACHRP document addresses the relatively uncommon practice of charging human subjects for one or more portions of their participation in studies.

We presented initial portions of this document in our January, 2020, issue (article 2, page 3), May, 2020, issue (article 4, page 5), and December, 2020, issue (article 3, page 4).

We resume here with:

"The preamble to 21 CFR Part 312 and 316 'Charging for Investigational Drugs Under and [i.e., 'an'] Investigational New

Application: Expanded Access to Investigational Drugs for Treatment Use; Final Rules,' states the following:

General Requirements for Charging: First, charging should be allowed only to facilitate development of a promising new drug or indication that might not otherwise be developed, or to obtain important safety information that might not otherwise be obtained.

The preamble to the 1987 charging rule made clear that there should be compelling justification for taking the unusual step of allowing charging for unproven therapy during its development, stating that 'cost recovery is justified in clinical trials only when necessary to further the study and development of promising drugs that might otherwise be lost to the medical armamentarium'" (SACHRP recommendations to HHS; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/november-20-2019-attachment-a/index.html).

Research Should Be Reviewed By IRBs

"These FDA regulations provide reasoning that could be adopted by IRBs to assist in the analysis of pay-to-participate research proposals. Most importantly, the FDA approach acknowledges that pay-to-participate trials should be unusual and require compelling justification.

No other U.S. regulations governing human subjects research directly address the issue of pay-to-participate trials. However, some of the IRB criteria for approval at 45 CFR 46.111 and 21 CFR 56.111 are relevant, as are certain consent requirements.

SACHRP acknowledges that there will be proposed research that is unregulated because it is not federally funded and does not involve an FDA-regulated drug, device or biologic. The committee believes that, because of the particular issues raised by trials that require participants to pay, such trials should be voluntarily submitted to an IRB even when there is no regulatory requirement.

Beneficence

First, 45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2) directs IRBs to approve proposed research only when:

Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

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

The validity of the science supporting a research proposal is relevant to the 'knowledge that may reasonably be expected to result,' which in turn influences whether it is appropriate to expose subjects to the burdens and risks of harm associated with the research" (supra at pp. 4-5).

Study Design Danger Signs for IRBs

"There are several reasons why a pay-to-participate trial may not have an acceptable level of scientific validity. First, if a study has not been vetted through traditional funding and peer review mechanisms, such as prior review by a study section or industry sponsor, it may be lacking in scientific merit, and exposing subjects to risks and burdens in the context of bad science is ethically unacceptable.

Scientific rigor may also be affected by the fact that pay-to-participate trials may entail an incentive to use less rigorous study design and avoid research methods such as randomization and blinding so that the paying subjects can be ensured access to the desired investigational product.

Moreover, there may be a conflict in favor of including paying subjects who can help meet funding goals even though they should be excluded for reasons of scientific validity or safety.

Finally, some subjects who are so motivated to enroll that they are willing to pay may have reason to deceive the researcher about eligibility, study adverse events, and other such issues to avoid jeopardizing their enrollment and continued participation, especially when their motivation is the expectation of direct medical benefit" (supra at pp. 4-5). © {TBC}

OHRP Investigation of IRBs and Researchers

Project Title: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Trial - ***HRR Article #13***
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 unjustifiable risks to study subjects.

* * *

Consumer Advocacy Group Urges OHRP To Investigate Apparent IRB Failures

We continue here with more of the charges made by Public Citizen (PC) about unnecessary risks to human research subjects, including striking IRB review failures.

We resume with PC's final comments in their OHRP letter in the section of the CLOVERS analysis titled "D. Conclusions and requested actions."

In this section, PC describes to OHRP the key questions to be answered about the CLOVERS experiment.

PC also wants an explanation of the exact role of the PETAL research network in conducting the multisite studies, and how the PETAL IRBs were involved.

"(2) During its review of CLOVERS, did the PETAL Network Central IRB (and any other IRB that approved CLOVERS) ask the CLOVERS investigators to provide[:]

(a) a detailed description of the use of intravenous fluids and vasopressors in usual-care management of sepsis patients;

(b) evidence to demonstrate that the CLOVERS liberal fluids management strategy is used clinically by anyone for usual care of early septic shock; and

(c) clarification regarding the differences between usual-care management for sepsis and each of the two management strategies being tested in CLOVERS?

If so, how did the CLOVERS investigators respond to any such requests?

Finally, we urge OHRP to require NHLBI to place a moratorium on all other current PETAL Network clinical trials and any other NHLBI-funded clinical trials testing interventions in critically ill subjects until the systemic breakdowns that permitted the fundamentally flawed CLOVERS to be approved in the first place are fully understood and corrected" (in 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, pp. 11; on the Web at https://www.citizen.org/sites/default/files/2446.pdf).

Study Design Details Do Matter and They Can Affect Protection of Human Subjects

"Please note that the OHRP may share our complaint letter, with identifiers, with anyone. We will be posting a copy on Public Citizen's website as well.

Thank you for your prompt attention to this important matter regarding the protection of human subjects.

We look forward to the OHRP's thorough and careful investigations into the serious regulatory and ethical lapses related to CLOVERS.

Please contact us if you have any questions or need additional information" (ibid).

Following the end of the letter, PC added an "Enclosure A" ("Critical Analysis of the Design of CLOVER").

This enclosure is one of the most complete and detailed analysis that HRR has ever seen of the interplay between scientific experimental design factors and study methodology with the ethical aspects of human subjects research.

Even if one is not especially interested in the scientific aspects of CLOVERS (treating septic shock, blood chemistry, biochemistry, etc.), the related IRB issues can apply to numerous types of studies. Especially instructive are PC's detailed descriptions of how experimental design minutiae can affect human subject safety.

Next month in HRR, we begin our presentation of the highlights from the "Attachment A" to the OHRP letter. © **{TBC}**

FDA Warning

Warning Letter To: Honolulu, Hawaii IRB (HRR Part 1)
Investigation Period: Ended on July 15, 2008
Warning Letter Date: November 13, 2008
Noncompliance: IRB repeatedly failed to follow regulations; IRB eventually restricted by FDA Order, including termination of ongoing studies and FDA refusal to accept new study applications following investigations over five-year period

* * *

IRB Fails to Follow Regulations on Children

With this article we begin coverage of a highly instructive series of FDA investigations of an IRB in Hawaii. The IRB managed to continually violate different IRB requirements.

For example, this first of three Warning Letters describes how the IRB in question violated regulations covering five different aspects of protecting human subjects in research.

The investigation was launched by FDA's San Francisco office. As usual, at the end of the inspection, the FDA investigator presented the findings to the IRB.

Also discussed was the preliminary content of the regulatory violations as recorded on the FDA's form known as the "FDA 483" or "Form FDA 483." FDA stated that:

"The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report is discussed below:

1. Failure to determine that research involving children as subjects is in compliance with 21 CFR 50 Subpart D (21 CFR 56.111(c)).

The IRB reviewed studies that included children's participation but failed to determine and document compliance with 21 CFR 50 Subpart D. Examples of this failure include, but are not limited to, the following studies:

a. ... [redacted by FDA] study, ... [redacted by FDA].

b. ... [redacted by FDA] study, ... [redacted by FDA] and ... [redacted by FDA].

2. Failure to prepare, maintain, and follow written procedures for conducting initial and continuing review of research (21 CFR 56.108(a) and 21 CFR 56.115(a)(6), 21 CFR 812.62[,] and 21 CFR 812.66).

In order to fulfill the requirements of Part 56, each IRB shall prepare, maintain, and follow written procedures for conducting its initial and continuing review of research."

What Was That Study? Who Was In It?

"Furthermore, according to 812.2(b)(1)(ii), [for] abbreviated IDE requirements for studies of non-significant risk studies (NSR), a sponsor must submit an explanation as to why its device is a NSR device.

The IRB is required to review and approve, require modifications in, or disapprove all investigations covered by these regulations.

If an IRB determines that an investigation, presented for approval under 812.2(b)(1)(ii), involves a significant risk (SR) device, it shall notify the investigator and where appropriate, the sponsor (21 CFR 812.66).

Examples of this failure include, but are not limited to, the following:

a. Your IRB has no written procedure for determining the risk of each device. Your ... [redacted by FDA] appears to imply that all ... [redacted by FDA] devices are NSR devices.

A blanket statement does not fulfill the regulatory requirements that are noted above since risk determination is not solely related to the type of device but is made in accordance with the indication for use of the device and how the device is used in a particular study.

Therefore, you could theoretically have one type of device that is NSR in one study but SR in another.

b. ... [redacted by FDA] study ... [redacted by FDA], was approved on September 10, 2007, even though it did not list a title, a sponsor, results of previous research, subject selection, exclusion criteria, and provisions for managing adverse effects.

All these are initial [IRB] review requirements as described by your written procedures." © {TBC}

In Court

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 57)
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

* * *

"Voluntary Consent" Is Indispensable

We continue this month with the Court's examination of the famous Nuremberg Code and its relationship to current federal regulations on protecting human research subjects.

We concluded last month with a discussion of the *United States v. Stanley* case, in which a soldier who was unaware that he had been experimented upon with LSD by the Army lost his subsequent lawsuit.

> "The United States Military Tribunal established the Nuremberg Code as a standard against which to judge German scientists who experimented with human subjects. Its first principle was [that] the voluntary consent of the human subject is absolutely essential ….
>
> Justice Brennan then concluded that 'the United States Military developed the Code which applies to all citizens -- soldiers as well as civilians.'
>
> Justice Brennan characterized the government's experimentation on an unknown [unknowing] human subject as 'an intentional Constitutional tort' and ended his opinion with a phrase that would thereafter be associated with the right to be free from unethical experimentation.
>
> 'Soldiers ought not to be asked to defend a Constitution indifferent to their essential human dignity' ….
>
> Justice O'Connor, also dissenting, stated: 'No judicially crafted rule should insulate from liability the involuntary and unknowing human experimentation alleged to have occurred in this case ….'
>
> Justice O'Connor noted that the United States military played an instrumental role 'in the criminal prosecution of Nazi officials who experimented with human subjects during the Second World War … and the standards of the Nuremberg Military Tribunal used to judge the behavior of the defendants … stated that the 'voluntary consent of a human subject is absolutely essential … to satisfy moral, ethical, and legal concepts' ' " ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, p. 17).

Court Says Nuremberg Code Can Be Used in U.S. Lawsuits

"Accordingly, Justice O'Connor reasoned:

> If this principle is violated the very least that society can do is to see that the victims are compensated, as best they can be, by the perpetrators.
>
> I am prepared to say that our Constitution's promise of due process of law guarantees this much ….

In re Cincinnati Radiation, 874 F. Supp. 796 (S.D. Ohio 1995) is the first case to expressly hold that the standards of the Nuremberg Code may be applied in the courts of the United States.

Plaintiffs who had been the unknowing subjects in experiments on radiation exposure brought suit against investigators and institutions involved in the study.

In rejecting a motion for summary judgment, the court held that such claims were cognizable. In a section titled, 'The Nuremberg Code,' the court examined the history of the Doctors Trial, stating:

> The judges appointed by President Truman to hear the medical case were all American judges and lawyers …. The Nuremberg tribunal was asked to determine culpability … under 'the principles of the laws of nations as a result from the usages established among civilized people, from the laws of humanity, and from the dictates of public conscience ….' " (supra at pp. 17-18). © **{TBC}**

IRB Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** U.S. IRBs should take note of a recent notice from FDA on the ***agency's requirement for IRB reviews of "deidentified human specimens,"*** as follows:

> "The U.S. Food and Drug Administration (FDA) is reminding the diagnostic device industry that ***we require Institutional Review Board (IRB) review for all clinical investigations of devices that involve human subjects, including those that use leftover, deidentified human specimens in FDA-regulated studies***.
>
> This requirement pertains to data used to support an investigational device exemption, device marketing application, or submission to the FDA, including in vitro diagnostic (IVD) technical or analytical studies that use human specimens.
>
> For further explanation, see the *Human Subject Protection: Acceptance of Data from Clinical Investigations for Medical Devices 2018 final rule* (https://www.federalregister.gov/documents/2018/02/21/2018-03244/human-subject-protection-acceptance-of-data-from-clinical-investigations-for-medical-devices).
>
> The 2006 FDA guidance, *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable* (/regulatory-information/search-fda-guidance-documents/guidance-informed-consent-vitro-diagnostic-device-studies-using-leftover-human-specimens-are-not), ***does not exempt any investigations from IRB requirements***" ("Studies Using Leftover, Deidentified Human Specimens Require IRB Review -- Letter to Industry," October 18, 2021, p. 1; on the Web at https:// www.fda.gov/medical-devices/industry-medical-devices/studies-using-leftover-deidentified-human-specimens-require-irb-review-letter-industry).

For more information, contact: Dr. William Maisel, FDA's Director of the Office of Product Evaluation and Quality at 301-796-5550.

• **Food and Drug Administration.** Comments are ***due by January 24*** on the ***reporting and recordkeeping requirements for Investigational New Drug Applications*** (NDAs) contained in 21 CFR Part 312. This includes regulations for "Investigator INDs," "Emergency Use INDs," "Treatment INDs," etc. Details are in the FEDERAL REGISTER at 86 Fed. Reg. 67060, November 24, 2021.

For more information, contact: FDA's Domini Bean in the Office of Operations, at 301-796-5733, or send email to PRAStaff@fda.hhs.gov.

• **Food and Drug Administration.** Effective on ***November 23, 2021***, Maytee Liedo is ***permanently barred*** from:

> "… providing services in any capacity to a person that has an approved or pending drug product application …. From about September 2013 through June 2016, Ms. Liedo and others ***conspired to unlawfully enrich themselves by making materially false representations about clinical trials***, fabricating data and the participation of subjects in those clinical trials, concealing from FDA, sponsors, and contract research organizations the fact that the ***data and participation of subjects had been fabricated***, and inducing sponsors and contract research organizations to pay money for Ms. Liedo and co-conspirators' own benefit" (86 Fed. Reg. 66567, November 23, 2021).

Liedo was a receptionist at Sacred Heart Medical Office, P.A., a private medical practice in Florida. For more information, contact: FDA's Jaime Espinosa at 240-402-8743, or send email to debarments@fda.hhs.gov.

• **National Institutes of Health.** The NIH has announced the availability of supplemental funding for ***ethical input*** into existing grants/contracts involved in the BRAIN Initiative.

> "Examples of relevant activities that integrate ***neuroethics*** perspectives may include but are not limited to ….
>
> • The ethical implications of access to and use of emerging neurotechnologies and ***their relationship to informed consent*** …."
> ("Notice of Special Interest (NOSI): Administrative Supplements for Embedded Ethicists into BRAIN Initiative Supported Research," November 19, 2021; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-MH-22-040.html).

For more information, contact: NIMH's James Churchill at 301-443-3621, or send an email to churchillj@mail.nih.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.

• **February 8-9, 2022**, in Orlando, Florida, and Virtual: **"14th Annual Enrollment Planning and Patient Recruitment."** Topics include: the needs of different patient populations, challenges of informed consent processes, and the use of digital technology to facilitate patient recruitment and retention in the conduct of clinical trials. Contact: Conference Registrar, Cambridge Healthtech Institute, 250 First Avenue, Suite 300, Needham, MA 02494 at 781-972-5400, or fax at 781-972-5425, or send email to chi@healthtech.com.

• **March 30-31, 2022**, Newport Beach, California: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP."** The topics include informed consent requirements, the ethics of clinical research related to patient treatment, and the duties and responsibilities of IRBs. Conference is presented by the Society of Clinical Research Associates (SoCRA). Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **April 28-29, 2022**, in Savannah, Georgia: **"15th Annual Device Research & Regulatory Conference."** The topics include using human factors engineering to reduce medical errors, physiological research, US versus EU research regulations, the role of IRBs in reviewing device research, FDA inspections of IRBs, and COVID-19 and human subjects research. This conference is presented by the Society of Clinical Research Associates (SoCRA). Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **May 1-4, 2022**, in Boston, Massachusetts: **"MAGI's Clinical Research Hybrid Conference - 2022 East."** Conference will be presented by MAGI (Model Agreements & Guidelines International). Meetings will be held at the Sheraton Boston Hotel, with optional live streaming or mobile access as well. Topics include: recent developments in human subjects protection regulations, government inspection of research sites, adverse event reporting, human subject recruitment, weighing risks vs. benefits for human subjects, and IRB best practices. Contact: MAGI Chairman Norman Goldfarb, Chairman at 650-465-0119, or send email to ngoldfarb@magiworld.org, or see their Web site at www.magiworld.org. ©

Dennis Maloney, Ph.D., is 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 Focus Surveys® .com and at MyLuckyPenny®.com.

Kathleen Maloney, M.Ed., is the Associate Editor of the Human Research Report. Her degree is in Computers in Education and she is a former Honors English teacher. She has published nationally, won competitive grant awards, and received a special award from the Alice B. Buffet Foundation (a Warren Buffet Foundation). Also a mixed media artist, a selection of some of her works is available on the Web at KathleenMaloney.net.