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Human Research Report™

PROTECTING RESEARCHERS AND RESEARCH SUBJECTS

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FDA's Advice for IRBs on How To Cope With the Coronavirus (#8)

We continue here with a very useful set of recommendations for IRBs on subject protection issues during the COVID pandemic. The relevant FDA guidance is 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 from where we left off last month with the final few comments from FDA on what to do with submissions of applications for IDE studies. However, we will then devote more attention to the next Q&A from the guidance on particular aspects of human research subject safety in medical device experiments.

"**For IDE studies**, the sponsor should submit a supplement to its existing IDE, with the following information added to the cover letter in the subject line:

CHANGE IN PROTOCOL SUPPLEMENT -- COVID-19 or NOTICE OF IDE CHANGE -- COVID-19, as applicable

TITLE OF PROTOCOL

The submission to the IDE should contain a tracked changes version of the protocol to facilitate review" (guidance, rev. December 4, 2020, p. 11; on the Web at https://www.fda.gov/media/136238/download).

Is Virtual Study Visit Needed for Safety?

"**Q5. Can a sponsor initiate virtual clinical trial visits for monitoring patients without contacting FDA if there is an assessment by the sponsor and investigator that these visits are necessary for the safety of the trial participant and it will not impact data integrity?**

FDA regulations allow for changes to be made to the investigational plan or protocol without prior FDA review or approval, if the change is intended to eliminate an apparent immediate hazard or to protect the life and well-being of trial participants.

Therefore, changes in protocol conduct necessary to immediately assure patient safety, such as conducting telephone or

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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video contact visits for safety monitoring rather than on-site visits, can be immediately implemented with subsequent review by the IRB and notification to FDA.

Since this reflects a protocol deviation (until the amendment is approved), documentation of the required deviations, as described above, would generally be acceptable (i.e., a document that lists each deviation, study reference ID, patient ID, and date).

For example, documenting that all protocol-specified visits will be done by telephone contact rather than on-site visits, and that procedures requiring in-person visits will either not be conducted, or performed by other means (specified, as appropriate).

Since the change to telephone or video contact visits would likely result in some protocol-required procedures not being conducted (e.g., vital signs, blood samples for safety laboratory studies), the sponsor must evaluate the potential impact on patient safety, and consider how to mitigate risks to patients, including the need to discontinue the investigational product" (supra at p. 12).

COVID and Collection of Data

"For IDE studies, sponsors are required to report deviations implemented to address the imminent safety risk to FDA within 5 working days after learning of the deviations.

We recognize that challenges related to the COVID-19 pandemic may make it difficult to meet this timeframe. Sponsors may consolidate implemented deviations when submitting 5-day reports and should update FDA as soon as possible.

Q6. With the rapid changes in clinical trial conduct that may occur due to the COVID-19 public health emergency, including multiple deviations to address patient safety, what is the best way for sponsors and investigators to capture these data?

As noted in the main body of this guidance, it is important to capture *specific* information for individual participants that explains the basis for missing protocol-specified information that includes the relationship to COVID-19 (e.g., from missed study visits or study discontinuations due to COVID-19) ....

If it is not possible to capture this information in the case report form(s), sponsors may develop processes that enable systematic capture of these data across the sites in a manner that enables the appropriate analysis when the data are submitted to FDA ...." (ibid).

When Protocols Need Not Be Amended

"Q7. If patients are currently dispensed investigational product through a pharmacy at the clinical trial site for self-administration at home, can a sponsor switch that to home delivery without amending the protocol?

If there is concern about risk of exposure to COVID-19, home delivery of investigational product that would not raise any new safety risks may be implemented to protect patients from coming to clinical trial sites ....

If the protocol indicates pharmacy dispensing for self-administration at home, and this is changed to direct-to-patient shipments, then a protocol amendment would be required to permit home delivery of investigational product.

If the extent of home delivery is limited to certain participants and not the entire population described in the protocol, documenting the change in the mechanisms of distribution of investigational product administration through protocol deviations may also be acceptable. If the change in the mechanisms of investigational product distribution is then included in a protocol amendment, such a change may be part of a 'cumulative' amendment that includes a number of changes that accrue, rather than [as] an urgent protocol change" (supra at pp. 12-13). © {TBC}

IRBs and Assessment of Benefit-Risk Ratios (#2)

We continue here with more FDA advice for IRBs and others on the assessment of benefit-risk ratios in human subjects research. The relevant guidance is titled "Benefit-Risk Assessment for New Drug and Biological Products."

We resume with the agency's concluding statement from the guidance's section on the crucial role of uncertainty in weighing benefit-risk ratios.

FDA notes in this regard that it is flexible when it comes to judging whether benefit-risk ratios have been accurately gauged by IRBs and researchers, especially in early Phase 1 studies for rare diseases.

> "This flexibility means that to be respectful of patients' willingness to participate in studies, it is important to maximize the potential for such clinical trials to provide interpretable scientific evidence about the drug's benefits and risks beginning from the earliest stages of drug development" (guidance, September, 2021, p. 11 of 20; see https://www.fda.gov/media/152544/download).

Patients Are Expert in Experience of Their Disease

> "Patient contribution is optimized in small sample size studies by minimizing bias and maximizing precision with trial design features such as randomization, blinding, enrichment procedures, and adequate trial duration. [FDA adds this note due to the fact that rare disease research often involves small sample sizes in the earliest stages.]
>
> **C. The Role of Patient Experience Data in FDA's Benefit-Risk Assessment**
>
> FDA recognizes the importance of enabling meaningful patient input to inform drug development and regulatory decision-making, including in the context of FDA's benefit-risk assessment.
>
> Patients are experts in the experience of their disease or condition, and they are the ultimate stakeholders in the outcomes of medical treatment. Patient experience data can inform nearly every aspect of FDA's benefit-risk assessment throughout the drug lifecycle, including:
>
> • Therapeutic context, such as:
> - Impact of the disease and its treatment on the patient
> - Patients' perspectives about available treatments and unmet medical needs
> - Enhanced understanding of the natural history of the disease or condition, including progression, severity, [and] chronicity
> - Potential benefits that are most meaningful
>
> • Acceptability of risk and uncertainty [and]
>
> • Value and burden of risk mitigation efforts" (ibid).

FDA View Similar to "Patient-Reported Outcomes"

> "If a methodologically sound and fit-for-purpose[24] data collection tool(s) is used to collect patient experience data in a drug development program, the collected data can provide direct evidence regarding the benefits and risks of the drug and their importance to patients.
>
> [FN #24: Fit-for-purpose: a conclusion that the level of validation associated with a medical product development tool is sufficient to support its context of use ….]
>
> During premarket review, FDA indicates in review documentation whether relevant patient experience data are submitted as part of the application, and whether relevant information was not submitted in the application but has informed FDA review nonetheless ….
>
> As discussed in section II, FDA must balance the perspectives of patients with the judgments it must make regarding overall benefit-risk of a drug to the patient population.
>
> For example, even if some patients may derive benefit from a drug and express the desire for access to a drug, FDA would not approve the drug if it FDA concludes that the drug would lead to more harm in the indicated population overall -- for example, if the drug is associated with significant risk, benefit is likely to be limited, and there is no way to identify those individuals who might benefit through the use of predictive biomarkers or other means" (supra at p. 12). © {TBC}

IRBs and Researchers' Use of "Real-World Data (RWD)"

Just as is true for IRBs' consideration of "Patient-Reported Outcomes (PROs)," IRBs continue to face the emergence of new ways of defining, using, and monitoring nontraditional data collection methods.

In turn, this means that applicable IRBs may have to alter how they review certain protocols.

Aside from any interest one may have in a particular scientific discipline or subject matter addressed in an experiment, human subject safety issues themselves remain crucial for IRB reviews of study protocols.

Hence, we address here the topic of "Real-World Data (RWD)" in this introductory article for IRBs.

Note, however, that we focus primarily on the human subject safety aspects of RWD rather than on the entire area of RWDs or on any particular subject matter being studied.

In the present article, we present highlights from the draft guidance titled "Considerations for the Use of Real-World Data [RWD] and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products."

"RWD" Applies to Various Clinical Study Designs

> "This guidance discusses the applicability of FDA's investigational new drug application (IND) regulations to various clinical study designs that utilize real-world data (RWD), and clarifies the Agency's expectations regarding clinical studies using RWD submitted to FDA in support of a regulatory decision regarding the effectiveness or safety of a drug (e.g., as part of a new drug application or a biologics license application) that are [sic] not subject to the IND regulations" (86 Fed. Reg. 70131, December 9, 2021).

Before proceeding further, note that FDA will accept comments on this draft guidance until March 9.

For more information on giving feedback to the FDA on this guidance, contact: Dianne Paraoan of FDA's Center for Drug Evaluation and Research at 301-796-3161, or send email to Dianne.Paraoan@fda.hhs.gov.

Our main interest in this new guidance lies with the subsection titled "5. Safety Reporting." The procedures described in this portion, or some reasonable procedural variation thereof, would be the types of steps that a reviewing IRB might want to see in a protocol.

This would be especially true for any postmarketing experiments or proposed monitoring activities.

> "• Applicants of NDAs [New Drug Applications] and BLAs [Biologics License Applications] and other responsible parties are subject to regulatory requirements regarding postmarketing safety reporting.
>
> Given that non-interventional studies examine the use of a drug in routine medical practice, the Agency requires that relevant adverse events be submitted to FDA in accordance with postmarketing safety reporting regulations.[17]
>
> [FN #17: See §§314.80 and 314.81 and 21 CFR 600.80.]" (guidance, December, 2021, p. 7 of 9; on the Web at https://www.fda.gov/media/154714/download).

Sponsor Reporting Requirements For Studies' Adverse Events

> "• For non-interventional studies, FDA recognizes that sponsors will often use only a subset (often called an analytic dataset) of a larger real-world dataset to conduct their analyses to support labeling changes.
>
> For example, a larger dataset may contain information regarding a product's approved and unapproved uses in clinical practice.
>
> If the sponsor is conducting a study to support a specific labeling change (e.g., a new indication), FDA does not expect the sponsor to search the entire database regarding all uses of the product for adverse events that would meet the reporting requirements under FDA's postmarketing reporting regulations.
>
> Nonetheless, if a sponsor identifies adverse events that are subject to postmarketing reporting requirements during the course of conducting a non-interventional study, such events must be reported in accordance with applicable postmarketing reporting requirements" (ibid). ©

IRBs and the Use of Convalescent Plasma (#1)

The use of "convalescent plasma" from former COVID-19 patients has received considerable attention in the public press. But what does this mean for researchers and IRBs?

Since the plasma use is not yet approved by the FDA, such a treatment is still considered experimental. Thus, the usual human subject protections apply to its use in any study.

However, there is more to this picture than just that simple statement. Recently, the FDA issued its final version of a guidance in this area. The new version, titled "Investigational COVID-19 Convalescent Plasma," was released on February 11 of this year.

In the present HRR article, we present a basic introduction from this new final guidance. We will devote more attention to the guidance's various sections that are most relevant for IRBs in future HRRs.

When Can Convalescent Plasma Be Donated?

"FDA is issuing this guidance to provide recommendations to health care providers and investigators on the use of COVID-19 convalescent plasma or investigational convalescent plasma during the public health emergency ….

We have revised the guidance to reflect that the EUA [Emergency Use Authorization] authorizes COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment in either the outpatient or inpatient setting[3].

[FN #3: Denise M. Hinton, U.S. Food & Drug Admin., U.S. Dep't of Health & Human Servs., Emergency Use Authorization for COVID-19 Convalescent Plasma ... available at https://www.fda.gov/media/141477/download).]

… [FDA now recommends] that individuals qualify as COVID-19 convalescent plasma donors 10 days following complete resolution of symptoms" (guidance, p. 2; on the Web at https://www.fda.gov/media/136798/download). © **{TBC}**

IRBs and Core PROs in Cancer Clinical Trials (#5)

With this article, we conclude our coverage of the FDA guidance titled "Core Patient-Reported Outcomes [PROs] in Cancer Clinical Trials." We resume with the agency's concluding recommendations for IRBs and researchers on trial design considerations that can affect human subject safety and potentially even invalidate an entire study if not heeded sufficiently.

"Schedule of administration [of the experimental product] should be taken into account, and assessments and their analysis harmonized so as not to obscure the results of either arm.

In the case where both arms have orally administered treatments on a daily schedule, assessments could be less frequent given the lack of cyclic variability surrounding administration schedules seen with IV chemotherapies" (guidance, June, 2021, p. 7; on the Web at https://www.fda.gov/media/149994/download).

Missing Data Can Be a Problem

"**B. Other Trial Design Considerations**

The following should be considered to mitigate missing data and improve the interpretability of PRO results:

- Prospectively establish procedures for mitigating missing data, including training for investigators and patients, a completion monitoring strategy, and obtaining PRO data from patients at time of early withdrawal. Include these procedures in the protocol.
- Methods to lessen patient burden should be explored, including use of electronic PRO capture that may allow for assessments outside of the clinic [especially during the COVID pandemic]. Sponsors should document how and when patients completed their PRO assessments (e.g., at home, in office, etc.).
- Reasons for missing PRO data should be documented and included in the analysis dataset.
- Provide a pre-specified plan for the analysis of PRO data including the threshold for and interpretation of a meaningful change in score(s), if relevant" (ibid). ©

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 - Charging Subjects for Clinical Trial Participation" - *HRR Article #4*
Document Source: Attachment, Letter to Alex Azar, Secretary, Department of Health and Human Services
Document Date: November 20, 2019
Available At: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/november-20-2019-attachment-a/index.html

* * *

IRBs Have Special Factors to Consider Regarding Subject's Ability to Pay

We continue this month with more advice for IRBs from the SACHRP on charging human subjects for their participation in experiments.

We begin with the committee's concluding recommendation on the role of the "beneficence" principle in human subject protections.

This final statement regarding the role of "beneficence" refers to the fact that some subjects who may be so motivated to enroll that they're willing to pay also may be motivated enough to lie about their eligibility. SACHRP warns that:

> "Failure to provide accurate information to researchers could create risks both to those subjects and to other participants.
>
> Conversely, some subjects who are required to pay to participate might be more invested and engaged in the research and thus might comply more closely with the trial requirements.
>
> These empirical considerations should be evaluated with evidence. [We now consider the principle of Justice.]
>
> **Justice**
>
> Regulations at 45 CFR 46.111(a)(3) and 21 CFR 56.111(a)(3) address the principle of justice, directing IRBs to assess whether:
>
> Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted.
>
> The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons" (p. 5).

Research Subjects May Be Desperate

> "One purpose of this regulatory provision aims at avoiding the inclusion of subject populations solely on the basis of convenience and control, which could result in unfairly concentrating research risks and burdens in certain vulnerable populations.
>
> Rather than targeting individuals who are economically disadvantaged, however, which may be of concern in some research, pay-to-participate trials are likely to selectively include individuals who are economically able to pay or raise the required funds.
>
> These individuals may be vulnerable in other ways. For example, they may be desperate if they have exhausted all available treatments for a serious condition, and thus may be vulnerable to exploitation.
>
> The regulatory provision's reference to consideration of whether the selection of subjects is equitable means that not only should the risks and burdens of research be fairly distributed, but so should the potential benefits.
>
> To the limited extent that pay-to-participate research offers the prospect of direct benefit to participants, the possibility of benefit as a participant should not be concentrated only in certain advantaged groups.
>
> This concern about pay-to-participate trials is different from the concern about fair distribution of benefits after an experimental intervention has been shown to be a successful treatment, but it should still be considered, since those who cannot afford to pay will be excluded from potential benefits in both instances.
>
> The economically disadvantaged may also go to great lengths to gather the resources

needed to participate, for example through crowdfunding and perhaps undertaking debt, if the potential for benefits appears sufficiently great" (supra at pp. 5-6).

Who Can Afford to Be a Research Subject If Participation Has a Fee?

"Whether it is appropriate to concentrate the potential benefits of pay-to-participate trials only in the economically advantaged raises an additional concern relating to scientific validity:

Are those who are economically advantaged enough to pay the costs of participation sufficiently representative and diverse so that study results will not be inappropriately biased by the exclusion of those unable to pay?

That is, will the research data be broadly applicable to a diverse cohort of future recipients?

To address this concern, IRBs will need to consider the likely study population as part of its evaluation of the proposal's scientific validity.

If that is acceptable, then special consideration should be given to subject vulnerability and inclusion.

Importantly, efforts to make recruitment fairer should also help promote generalizability and scientific validity.

Finally, pay-to-participate trials may also reduce trust in science by fostering the perception that research participation is a valuable commodity made unfairly available to those individuals with more resources.

Furthermore, these trials might divert resources (both financial and human capital) from better research proposals or better treatments for subjects.

Autonomy and Informed Consent

Regulations at 45 CFR 46.116(a) and 21 CFR 50.20 require that investigators seek informed consent 'under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.'

In addition, 45 CFR 46.116(c)(3) and 21 CFR 50.25(b)(3) require that informed consent disclose 'any additional costs to the subject that may result from participation in the research.'

This has clear applicability to pay-to-participate trials, as the costs must be disclosed to subjects.

Because the primary goal of research is to create generalizable knowledge that may benefit patients in the future, subjects in pay-to-participate trials are asked to contribute to societal benefit both by their data and by their financial payment.

Subjects have many and often mixed reasons to enroll in research studies, including altruism and a desire for anticipated direct clinical benefit.

The requirement to pay in order to participate in research will probably be a disincentive to many potential subjects, either because they are aware that research is usually cost-free to subjects and may even involve payment to them, or because they do not have sufficient funds" (supra at p. 6).

Charging for Subject Participation May Produce False Value Impression

"However, pay-to-participate trials pose a heightened risk of fostering the therapeutic misconception, either intentionally or not, as compared with traditionally funded studies.

When subjects are asked to pay to participate, they may view the amount charged as a signal that participation itself is valuable -- and because price often connotes value, higher prices may signal higher value.

Moreover, because asking subjects to pay to participate is unusual among clinical trials, subjects may be more likely to view participation as something desirable and payment as an exchange for some benefit.

In particular, pay-to-participate trials may exploit vulnerable patients, those for whom clinical care options may have been exhausted and who are understandably desperate to find something that works.

Asking them to pay may not only confuse research with clinical care and encourage therapeutic misconception; it may also encourage financial risk-taking in hopes of a highly unlikely medical outcome" (supra at pp. 6-7). © {TBC}

OHRP Investigation of IRBs and Researchers

Project Title: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Trial - ***HRR Article #14***
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.

* * *

IRB Factors Apply to Many Types of Studies

As we noted last month, the Appendix of the above-cited letter to OHRP that claimed so many regulatory failures contains one of the most detailed analyses that we've ever seen of how research design elements can affect the protection of human subjects.

Therefore, even if one is not interested in the particular studies in question, the inherent IRB lessons are valuable for many disciplines and research paradigms.

We begin here with Public Citizen's (PC's) explanation of the CLOVERS' basic experimental design, as follows:

"***Introduction***

The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial (CLOVERS)[1,2] is a multicenter, randomized, unblinded, two-arm clinical trial presently being conducted by a group of academic hospitals called the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network,[3] previously known as the Acute Respiratory Distress Syndrome (ARDS) Network.[4]

[FN #1: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf. Accessed August 22, 2018.

FN #2: Self WH, Semler MW, Brown SM, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: Rationale for a randomized trial. Ann Emerg Med. 2018 May 9. pii: S0196-0644(18)30315-9. doi: 10.1016/j.annemergmed.2018.03.039. (Epub ahead of print).

FN #3: PETAL Network: Prevention & Early Treatment of Acute Lung Injury. http://petalnet.org/. Accessed August 22, 2018.

FN #4: NHLBI ARDS Network. About the NHLBI ARDS Network. http://www.ardsnet.org/. Accessed July 12, 2018.]" (in 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, Appendix, p.1; on the Web at https://www.citizen.org/sites/default/files/2446.pdf.)

Basic Premise That Justifies Experiment Is Refuted

"Funding for CLOVERS is provided by the National Heart, Lung, and Blood Institute. The primary objective of the trial is to compare the effect on mortality of an early *liberal fluids-restrictive vasopressors* management strategy (liberal fluids group) (See Figure A1, Appendix) with an early *restrictive fluids-liberal vasopressors* strategy (restrictive fluids group) (see Figure A2, Appendix) in patients with sepsis-induced hypotension.

The investigators claim that there is real debate among clinicians over which of these two strategies should be used to manage early sepsis.[5]

[FN #5: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) protocol. Version II. November 17, 2017. https://www.citizen.org/sites/default/files/clovers_protocol_versionii_111717_clean.pdf. Accessed July 12, 2018.]

However, the CLOVERS investigators provided no data that support this assertion. Specifically, the investigators failed to show directly that either management strategy is used, let alone preferred, by caregivers in the usual-care management of early sepsis." © {TBC}

FDA Warning

Warning Letter To: Honolulu, Hawaii IRB (HRR Part 2)
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

* * *

Why Bother With All Those Records?

We continue here with more of FDA's findings of a Hawaiian IRB's noncompliance with federal regulations on the protection of human research subjects, including:

"3. Failure to conduct continuing review of research (21 CFR 56.109(f)).

An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year.

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

a. Your records indicate that a progress report for ... [redacted by FDA] study, ... [redacted by FDA] has not been submitted within the last year.

Your January 24, 2008, correspondence requesting the report went unanswered and your subsequent correspondence was approximately three months later, on May 3, 2008.

That correspondence went unanswered as well. At the time of the inspection, you had taken no further action to address this.

b. Your records indicate that ... [redacted by FDA] study, ... [redacted by FDA] was approved by your IRB on September 6, 2004 ....

Your IRB does not have on file copies of the protocol, progress reports, or evidence of continuing review for this study; nor do you have documentation that the study was terminated."

"4. Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25 (21 CFR 50.25 (a)(1) and 21 CFR 50.25 (a)(4), 21 CFR 56.109(b)).

The IRB failed to ensure that informed consent documents contain all the information required by 21 CFR 50.25 such as an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental and a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

A New Kind of "Short Form" Consent?

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

a. The informed consent for ... [redacted by FDA] study ... [redacted by FDA] does not include a description of the procedures to be followed.

Specifically, it does not address the ... [redacted by FDA] that is required by the study protocol.

b. There was no disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, in the informed consent, for the following studies:

1. ... [redacted by FDA] study ... [redacted by FDA]
2. ... [redacted by FDA] study, ... [redacted by FDA].

5. Failure to prepare and maintain adequate documentation of IRB activities including copies of all research proposals reviewed, approved sample consent documents, and progress reports submitted by investigators (21 CFR 56.115(a)(1)); and, failure to maintain minutes of IRB meetings, including attendance at the meetings, actions taken by the IRB, the vote on these actions including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution (21 CFR 56.11 5(a)(2))." © {TBC}

In Court

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 58)
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

* * *

What Are the Basic Rights of Human Research Subjects?

We continue now with more of the arguments made by the former research subject's attorneys why her lawsuit should stand up in court. In particular, by citing the Nuremberg Code, the defense argued that the university, its IRB, and its researchers violated the constitutional rights of the high school student.

We resume with more of the discussion in court about the World War II's Nuremberg Code and why human research subjects have certain basic rights, even though there was disagreement on what those rights were during the "Doctors' Trial."

> "Throughout the trial, the question of what were or should be the universal standards for justifying human experimentation recurred.
>
> 'The lack of a universal principle for carrying out human experimentation was the central issue pressed by the defendant [Nazi] physicians throughout their testimony.' Id. quoting, *United States of America v. Karl Brandt*, et al., TRIALS OF WAR CRIMINALS, Vol. II at 181 (1949).
>
> After quoting the first principle of the Nuremberg Code, the [*Brandt*] court concluded: 'The Nuremberg Code is part of the law of humanity. It may be applied in both civil and criminal cases by the federal courts in the United States. The court thus held:
>
> If the Constitution has not clearly established a right under which these clients may attempt to prove their case, then a gaping hole in that document has been exposed.
>
> The subject of experimentation who has not volunteered is merely an object. The plaintiff in this case must be afforded at least the opportunity to present their case. *Id.*, at 822[']" ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, pp. 18-19).

"Right to Bodily Integrity" Is Basic Right

"The next case to invoke Nuremberg was *Stadt v. University of Rochester*, 921 F. Supp. 1023 (W.D.N.Y. 1996). In this case, plaintiff brought an action under the Federal Tort Claims Act claiming she had been the subject of testing by physicians who had injected her with plutonium without her informed consent.

In rejecting a motion that the constitutional claims should be dismissed, the court stated: 'This case does not involve the right to refuse medical treatment, but instead the right to be free from non-consensual experimentation on one's body, the right to bodily integrity … [a] right which has been recognized throughout this nation's history.' *Id.*

In support, the court reviewed the long line of cases holding that the right to bodily integrity, which would include the right to be free from unethical human experimentation, was a fundamental right. *Id.*, citing *Albright v. Oliver*, 510 U.S. 266 (1994), *Schmerber v. California*, 384 U.S. 757 (1966), *Skinner v. State of Oklahoma*, 316 U.S. 535 (1942), [and] *Union Pacific R. Co. v. Botsford*, 141 U.S. 250 (1891).

In *Heinrich v. Sweet*, 62 F. Supp. 2d 282 (D. Mass. 1999), family members brought an action based on allegations that various government doctors conspired to conduct extensive, unproven, and dangerous medical experimentation on 140 terminally ill patients without their informed consent.

The court stated that the issues presented must be understood in their historical context and then proceeded to describe the background of the Doctors Trial and the Nuremberg Code" (supra at p. 19). © **{TBC}**

IRB Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** FDA is reminding IRBs that they must review:

"… 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" ("Studies Using Leftover, Deidentified Human Specimens ***Require IRB Review***," October 18, 2021; on the Web at https://www.fda.gov/medical-devices/industry-medical-device/studies-using-leftover-deidentified-human-specimens-require-irb-review-letter-industry).

For more information, contact: William Maisel, MD, MPH, Director, Office of Product Evaluation and Quality, at 301-796-5550.

• **National Institutes of Health.** Effective ***January 17 through March 17,*** supplemental funds are available to support:

"1) ***research on bioethical issues*** to develop or support the development of an evidence base that may inform future policy directions, and/or 2) certain efforts to develop or augment ***bioethics research capacity***.

Applicants may propose to supplement parent awards focused on bioethics or to address a component related to bioethics in a biomedical research study" ("Notice of Special Interest (NOSI): Administrative Supplement for Research and Capacity Building Efforts Related to Bioethical Issues (Admin Supp Clinical Trial Optional)," December 16, 2021; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-026.html).

More than 20 different areas of interest are described in the NIH Notice.

• **National Institutes of Health.** Comments are ***due by February 16*** on the record keeping and reporting requirements of NIH's current procedures for granting requests for a Certificate of Confidentiality (CoC). NIH is proposing to make changes to its electronic application steps for CoCs.

"CoCs are issued … to authorize researchers ***to protect the privacy of human research subjects*** by prohibiting them from releasing names and identifying characteristics of research participants to anyone not connected with the research, except in limited circumstances specified in the statute" (86 Fed. Reg. 71651, December 17, 2021).

For more information, contact: Dr. Pamela Reed Kearney at 301-402-2512, or send email to NIH-CoC-Coordinator@mail.nih.gov.

• **National Institutes of Health.** ***Effective from January 25 onward***, applications for funding from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) ***must include certain information regarding involvement of human research subjects***. Replacing previous such NIH Notices, NIAAA now:

"... expects investigators and their institutions to ***provide plans for submitting grant-related human subjects data*** to a NIAAA-sponsored data repository, the NIAAA Data Archive ($NIAAA_{DA}$), as outlined in this Notice …

This policy applies to all NIAAA grant applications (new and resubmitted) that include human subjects research and all Funding Opportunity Announcements (FOAs) in which NIAAA participates, ***regardless of the direct costs*** requested in any year ….

The NIAAADA accepts only electronic, de-identified data from human subjects studies. ***This includes data from clinical trials, epidemiological surveys, human laboratory investigations, and other types of studies involving human subjects*** ….

This Notice ***substantially changes*** the data sharing expectations for genomic data and for data related to biosamples and genomic data" ("Notice of NIAAA Data-Sharing Guidance for Human Subjects Grants Research Funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (3rd Revision)," NIH Notice No. NOT-AA-22-003, December 16, 2021; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-AA-22-003.html).

For more information, contact: Daniel Falk, Ph.D., of NIAAA, at 301-443-0788. ©

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 FocusSurveys.com and at MyLuckyPenny.com.

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