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PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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# IRBs, the "Principle of Justice," and Public Mistrust of Science During COVID

Although this article focuses on IRBs and the "Principle of Justice," its intent is broader. As we will see, **IRBs may have a crucial role to play in countering public mistrust of science** and the refusal to vaccinate against COVID. But first ...

The ever-influential Secretary's Advisory Committee on Human Research Protections (SACHRP) has issued a new set of recommendations for IRBs. The relevant document is titled "Consideration of the Principle of Justice 45 CFR part 46."

We present here core segments of this new advisory and we will include more related details in future installments of our usual "IRB Recommendations by the SACHRP" feature.

> "Injustice has no place in human subjects research and undermines public trust in science[1].
>
> [FN #1: ... SACHRP represents the scientific and academic establishment, and inherits that enterprise's assumptions and biases. Justice in the practice of research on human subjects cannot be fully realized without trying to make these assumptions and biases explicit ....]" (SACHRP letter to HHS Secretary Xavier Becerra, J.D., July 22, p. 1; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-consideration-of-the-principle-of-justice-45-cfr-46.html).

## Current Distrust of Science In COVID Pandemic

> "[There are several terms, in particular, that we have used that may carry unintended meanings that are contrary to the intent of our recommendations.
>
> Science -- when we write about science, we are talking about systematic learning from observation or experiment. We are not talking about the academic, government[,] and commercial entities that embody institutional science.
>
> We mean science as a method that recognizes that truth is best approximated empirically, and that we must not accept

**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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the truth of our perceptions or beliefs without testing.]

One consequence of injustice, whether it manifests as inappropriate exclusion from participation or as exploitation of 'populations of convenience,' is the belief that human subjects research serves the interests of the privileged and powerful and therefore perpetuates economic, racial, religious, sexual, gender, and cultural biases.

The history of research on human subjects reflects numerous examples of the relationship between blindness to, or disregard of, issues of justice and consequent justified mistrust.

Most recently, the ongoing disparate economic and public health impacts of the COVID-19 pandemic, including issues related to vaccine equity and hesitancy, illustrate some of the sources and consequences of distrust in science and its social goals" (ibid).

## Potential Vital Role of Local IRBs

"Researchers and many others recognize human subjects research as a primary human activity dedicated to objectivity[2] and empiricism; however, it continues to be marred by unjust policies, practices, beliefs, and systems of power.

[FN #2: Objectivity -- objectivity and science are inseparable, but objectivity is aspirational. As people, we can only try to distance ourselves from our assumptions and beliefs, but true objectivity is impossible.

There are two reactions to that impossibility -- we can declare objectivity unattainable and therefore without value, but such a reaction condemns us to knowingly embrace one set of assumptions as better than another, a strategy that cannot but lead to conflict and division.

Or we can keep trying to identify and eschew our assumptions to try to build a common understanding where the only assumptions come from our collective humanity.]

It is time to reconsider and reestablish justice as a core principle in biomedical and social-behavioral research, reflecting the reality that the science of people must be accountable to people to be legitimate ...." (ibid).

## Local IRBs Already Have Recognized Role

"Human Research Protection Programs (HRPPs) and Institutional Review Boards (IRBs) have a limited but important role to play, and the recommendations in this document are intended as a starting point from which to develop more detailed policies and practices to help ensure fair access[3] to opportunities for research participation and reasonable assurance that the potential benefits from research are available and meaningfully applicable to all.

[FN #3: ... it is a core ethical tenet that research participation must be voluntary. Thus, opportunities must be available, but individuals must also have reason to participate.

Our recommendations largely address access, which is a necessary prerequisite, but articulating the goals of research in a way that is compelling to historically excluded communities is likely to require time and the rebuilding of trust, which will only happen through practice.]" (pp. 1-2).

In HRR's opinion, continued communications from individual national spokespersons citing numbing numbers will do nothing whatever to change public mistrust of science into trust.

There's an old saying that "all politics are local." Changing public mistrust of science to at least a grudging trust must come from local sources too … like from thousands of local IRBs and similar local "neighbors" -- not from national spokespersons, no matter how well-intentioned.

Now may be the best time for local IRB members to speak up for science, protect individual rights as they already have for decades, and thereby save lives by encouraging vaccinations against COVID-19.

The tens of thousands of local IRB members throughout the U.S. would thus expand their legacy of protecting individual rights while still supporting science more than ever before. © {TBC}

# IRBs, COVID, and Experiments With New Drugs/Biologics (#3)

We continue this month with more tips for IRBs and researchers from the FDA's guidance titled "COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention." These tips can affect various aspects of IRB reviews.

We resume with more advice from the guidance subsection titled "B. Trial Design and Conduct Considerations," as follows:

"• Master protocol sponsors should seek concurrence from the Agency before implementing a change where a drug evaluated under the master protocol is incorporated into the trial as either background therapy or as part of the control arm.

It is possible that a drug may be incorporated into the control arm but not as background therapy for all arms in situations where it would be inappropriate to add therapies together (e.g., similar mechanism of action).

• For master protocols evaluating multiple drugs some participants may not be eligible to receive a particular drug for safety reasons (e.g., diminished renal or liver function).

In these situations, protocols should be designed to prevent participants from being randomized to drugs they are not eligible to receive" (guidance, May, 2021, p. 5; on the Web at https://www.fda.gov/media/148739/download).

## The Importance of Blinding

"• Master protocol sponsors should make every effort to incorporate blinding into their trials. Sponsors should consider the following:

- In a placebo-controlled trial where investigational drugs have multiple routes of administration or variable dosing schedules, blinding could be achieved through either of the following:

• A multiple-dummy (e.g., for a master protocol with three investigational arms, a participant will receive three placebos or one investigational drug and two placebos, leading to complete blinding).

or

• A distinct, blinded placebo control for each drug (e.g., for a master protocol with three investigational arms a participant will receive one substance, either the investigational drug randomized to or its matching placebo).

In this case, the sponsor could randomize the participants to an intervention-specific subprotocol (among those they are eligible for) and then randomize them to either that investigational drug or its matched placebo" (supra at pp. 5-6).

## Importance of Human Subject Safety Data

"Statistical comparisons between an investigational drug and placebo can include participants who were eligible to be randomized to the drug but were randomized to placebo groups for other interventions.

- In trials where blinding is impractical, FDA strongly recommends an objective endpoint (e.g., all-cause mortality).

• In cases where drugs are intended to affect different aspects of the disease (e.g., anticoagulants, antivirals), there may be multiple intervention-specific endpoints.

Master protocol sponsors should discuss endpoint selection with the Agency, given the potential for additional complexities in trial design, conduct, and analysis.

• Collection of safety data in important for novel drugs as well as repurposed drugs being evaluated for COVID-19, as the safety profile of repurposed drugs may differ in a new population.

However, under certain circumstances and with the Agency's concurrence, a selective approach to safety data collection for drugs with a well-characterized safety profile and low toxicity may be appropriate.[13]

[FN #13: See *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (Feb. 2021) and *Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Post-approval Clinical Investigation* (February, 2016).]" (supra at pp. 5-6). © {TBC}

# IRBs and Hospital-Acquired Bacterial Pneumonia (#6)

We conclude our coverage now of the current final guidance from FDA titled "Hospital-Acquired Bacterial Pneumonia [HABP] and Ventilator-Associated Bacterial Pneumonia [VABP]: Developing Drugs for Treatment." These particular types of risks grow as COVID continues.

Inappropriate selection and/or use of statistics can invalidate a study and potentially expose human subjects to unnecessary risks if the study becomes invalidated. We resume our coverage with the concluding note from *Subsection 10* ("*Trial Procedures and Timing of Assessments*"):

"c. Visits after completion of therapy

The protocol should specify evaluations for continued clinical response or resolution of HABP/VABP and safety at approximately 7 to 14 days after patients complete antibacterial therapy. Sponsors should assess and report mortality, including a mortality assessment at day 28.

*11. Statistical Considerations*

In general, sponsors should provide, before trial initiation, a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation" (guidance, June, 2020, p. 8); on the Web at https://www.fda.gov/media/79516/download).

## Definitions of Different Patient Groups

"The primary efficacy analysis should be based on the difference between treatment groups in the proportions of success on the primary outcome measure, assessing either noninferiority or superiority.

a. Analysis populations

The following definitions apply to various analysis populations:

- Intent-to-treat (ITT) population -- All randomized patients.
- Safety population -- All patients who received at least one dose of drug during the trial.
- Microbiological intent-to-treat (micro-ITT) population -- All randomized patients who have a baseline bacterial pathogen known to cause HABP/VABP that is susceptible to the investigational drug and active control, identified from an appropriate sputum or blood specimen.
- Per-protocol populations -- Patients who are not lost to follow-up and adhere to trial procedures as specified in the protocol.
- Per-protocol microbiologically evaluable populations -- Patients who are characterized in the per-protocol population and have a baseline bacterial pathogen identified as the cause of HABP/VABP" (supra at p. 9).

## Estimating Treatment Effects

"Sponsors should discuss with the Agency the prespecified primary analysis population before initiating the trial. In general, it is acceptable to consider the ITT population as the primary analysis population.

For antibacterial drugs with a narrow spectrum of activity (e.g., a drug active against a single genus and species of bacteria), the micro-ITT population will be considered the primary analysis population.

b. Noninferiority margins

Historical data support the appropriateness of noninferiority trials for HABP/VABP …. For example, with the use of survival endpoints, a noninferiority margin of 10 percent can be supported by the historical evidence, which supports a reduction immortality by effective therapy of about 20 percent.

A 10 percent noninferiority margin supports a preservation of a meaningful fraction of that effect. If a noninferiority margin >10 percent is selected, sponsors should discuss the rationale and justification with the Agency.

c. Sample size considerations

In one example of a sample size calculation, approximately 268 patients per group is estimated for the ITT analysis population based on the rate of all-cause mortality of 15 percent in the test and control groups and a noninferiority margin of 10 percent.

The trial will rule out greater than 10 percent inferiority of the investigational drug to the control drug (an upper bound of the two-sided 95 percent confidence interval for the difference in the rates of all-cause mortality of the control drug minus the investigational drug)" (supra at p. 9). ©

# IRBs and FDA's Advice on How To Cope With Coronavirus (#5)

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

Our focus in this article is on the 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."

Our most recent installment on this topic was in our January 2021 issue. For the foreseeable future, depending on other possible IRB-related developments, we will include highlights from this series of advisories on a continual basis.

## To Start or Stop Human Subjects Research

We resume here with more of FDA's response to Q#1 in its FAQ-style guidance.

**"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? …**

- Assessing the continued availability of, and support for, information technology systems and any other technological tools that are needed to support the trial.

  Are current contingency plans adequate for the types of disruptions that might be anticipated? What other plans can be put in place to minimize any potential disruptions?

- Assessing whether there will be continued operations of, and adequate communications with, IRB/IEC [Institutional Review Board/Independent Ethics Committee] and Data Monitoring Committee (DMC) staff, if applicable, to support trial needs.

- Assessing whether it is feasible to conduct the trial in light of any COVID-19 public health measures implemented by Federal and State authorities to control the virus.

  Involvement of a study's DMC, if one has been established, can provide support for the assessments discussed above.

  Since a primary responsibility of the DMC is assuring the safety of participating trial participants, the DMC's assessment of the impact of modifications of trial conduct due to COVID-19 on patient safety is important to consider" (Guidance, rev. December 4, 2020, pp. 8-9 of 35; on the Web at https://www.fda.gov/media/136238/download).

## Possible Benefit to Research Subjects Makes a Difference

"The risks and benefits of continuing a trial are likely different than a decision to initiate a trial (other than trials intended to evaluate investigational treatments or vaccines for COVID-19).

Given the evolving situation, with likely increasing impacts on investigators, staff, and supply chains, sponsors should carefully consider the ability to effectively mitigate risks such that patient safety and trial integrity are assured.

In addition, it is important to consider whether initiation of the trial could interfere with public health measures implemented by Federal and State authorities to control the virus.

**Q2. What key factors should sponsors consider when deciding whether to continue administering or using an investigational product that appears to be providing benefit to the trial participant during the COVID-19 public health emergency?**

There may be circumstances in which an investigational product (either a drug, biological product, or medical device) appears to be providing benefit to the trial participant.

A sponsor deciding whether to continue administering or using such a product during the COVID-19 public health emergency should carefully consider context-dependent issues, including whether a trial participant appears to be benefitting from treatment with the investigational product, whether there are reasonable alternative treatments, the seriousness of the disease or condition being treated, and the risks involved in switching to an alternative treatment if necessary" (supra at p. 9). © {TBC}

# IRBs and Signature Waivers For Clinical Researchers (#5)

With this article we conclude our coverage of the highlights of two companion FDA guidances for IRBs and others titled "Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions -- Statement of Investigator (Form FDA 1572)" (May, 2010; at https://www.fda.gov/media/78830/download), and "Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions -- Statement of Investigator (Form FDA 1572) (Revision 1)" (May, 2021; at https://www.fda.gov/media/148810/download).

These guidances can be invaluable in assisting IRBs in those situations where a researcher cannot or will not sign the otherwise routine Form FDA 1572 in which the researcher, among other things, agrees to abide by all applicable human subject protection regulations.

## Getting It All Done At Once

We resume with the conclusion of Q&A #45 that we presented in the August HRR from the 2021 FDA update on signature waivers, as follows:

> "45. … If a request for waiver of the 1572 signature includes the use of an independent ethics committee (IEC) instead of an IRB, then the sponsor should obtain IRB waiver approval first or submit both waiver requests in one submission.
>
> FDA recommends that if a sponsor intends to request both a waiver of the 1572 signature requirement and a waiver of the IRB requirement, the sponsor does so in one submission. In this submission, the sponsor should:
>
> 1. Explicitly state, in the cover letter subject line, that it is requesting both waivers (waiver of the Form FDA 1572 signature and waiver of the IRB requirement); and
> 2. Ensure that both the request for waiver of the 1572 signature requirement and the request for waiver of the IRB requirement contain all the information required to support each waiver request. The information supporting these requests should be separated and clearly marked" (May, 2021, guidance, p. 7). ©

# IRBs and New ANDAs During COVID Crisis (#1)

A newly revised guidance from FDA is designed to answer questions that the agency has been receiving regarding certain drug studies being attempted during the COVID crisis. The guidance is titled "Development of Abbreviated New Drug Applications During the COVID-19 Pandemic -- Questions and Answers."

> "FDA has received questions from prospective applicants and applicants of ANDAs about generic drug product development and application assessment during the COVID-19 public health emergency. FDA ... is providing ... responses in this guidance document for the benefit of all stakeholders" (April, 2021, rev. September 8, 2021; p. 2; on the Web at https://www.fda.gov/media/147355/download).

## Safety of Human Subjects and Study Staff

> "The questions and answers are presented in the following categories: A) generic drug product development; B) submission and assessment of ANDAs; and C) marketing and exclusivity ….
>
> The questions and answers in this section generally assume that bioequivalence (BE) studies being conducted to support the submission and approval of an ANDA have been delayed, interrupted[,] or have not started due to the COVID-19 public health emergency.
>
> As a result, prospective applicants are faced with difficulty obtaining reference products (i.e., the reference standard (RS), which in most cases also will be the reference listed drug (RLD)) or with expiring reference products and/or test products. The questions and answers in this section address those concerns.
>
> As a general matter, we recommend that prospective applicants take adequate precautions and have written procedures in place to ensure safety of study subjects and staff involved in the conduct of a BE study ....
>
> Prospective applicants also must submit required premarket reports, including all serious adverse event reports required under 21 CFR 320.1(d)(3)" (supra at pp. 2-3). © **{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.

* * *

## IRBs and Financial Compensation For Human Research Subjects (#9)

We continue here with more of our coverage of the SACHRP's recommendations for IRBs and researchers that are contained in SACHRP's letter to HHS as "Attachment A -- Addressing Ethical Concerns, Offers of Payment to Research Participants."

We resume with more of SACHRP's advice to IRBs listed under Section #5 of its recommendations regarding ways for IRBs and researchers to support "high-quality decision-making" on the part of human subjects via techniques such as:

"• Including tests of comprehension or 'teach-back' methods that will provide an indication that potential participants are aware of and understand key information about the study.

• Incorporating a waiting period for potential participants to reflect on their desire to participate and potentially discuss the study with trusted others.

• Facilitating explicit consideration of how a prospective participants' current interests may conflict with their future interests (for example, asking for reflection about the value to the individual of trading payment now for risks that may materialize into harms later).

• Providing further support for any individual who expresses that he or she 'has no choice' but to enroll, whether due to pressure from medical or financial needs.

SACHRP notes that the 'key information' requirement in the revised Common Rule may also promote these goals. Most important is the recognition that IRBs and investigators have a variety of mechanisms to help transform anyone like Potential Participant 2 at least into someone like Potential Participant 1 [see previous HRRs for these examples], avoiding concern about undue influence while still allowing incentive payments.

In other words, cogent consent forms and processes aimed at supporting and promoting informed decision-making can help minimize the likelihood that participants will be motivated to ignore or misunderstand key information because of the attractiveness of incentive payments" (from SACHRP letter to HHS Secretary Azar, September 30, 2019, pp. 8-9; on the Web at https://www.hhs.gov/ohrp/September-30-2019-letter-hhs-secretary.html).

## Summary of Recommendations for IRBs

"Importantly, the regulations do not require elimination of influence, but rather that investigators minimize the possibility of undue influence. From a practical perspective, the total elimination of any possibility of undue influence is likely to be infeasible or substantially overprotective, or to make research difficult or impossible to carry out.

Therefore, it should be neither the expectation nor the goal. Moreover, IRBs should make sure that any discomfort they have with incentive payments is not serving as a proxy for discomfort with the risks inherent in the study protocol.

Concern about incentive payments should not mask concern about allowing a research study to proceed at all.

In summary, IRBs should consider a number of factors when evaluating the acceptability of incentive payments:

• Their responsibility to approve research only when risks are reasonable in relation to benefits to participants and/or society;

• The possibility that incentive payments will compromise the informed consent process;

• Steps that can be taken to support autonomous decision-making in those contexts;

• Tradeoffs that may be associated with restricting incentive payments and how that may affect achieving adequate recruitment; and

• How similar payment might be viewed outside the research setting" (supra at p. 9). © {TBC}

# OHRP Investigation of IRBs and Researchers

**Project Title:** Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Trial - ***Article #10***
**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 Advocates Say Informed Consent Does Not Reveal Truth of Study

We continue here with more of Public Citizen's (PC's) analysis of what PC considers to be a significantly flawed study containing an unethical informed consent document, among other compliance failures.

The study is known as the multisite "CLOVERS" experiment.

We resume with more excerpts from the experiment's IRB-approved consent form, and PC's reaction to the consent excerpts, including this part of the experimenters' explanation to prospective human subjects about:

> "***Side effects and risks that are possible if you take part in this study***
>
> • Risk of Getting Extra Fluids: Patients in the (liberal fluids) group may get extra fluids through a tube in a vein ….
>
> • Risk of Getting Medicine to Raise Blood Pressure: Patients in the (restrictive fluids) group may receive earlier or more medicine to raise blood pressure ….
>
> ***Risks that are not known ….***
>
> Although both fluids through a tube in a vein and vasopressors are commonly used in the care of this condition …

[In its critique, PC said that] None of the above statements informs prospective subjects (or their legally authorized representatives) that both the liberal fluids and restrictive fluids management strategies are experimental and deviate substantially from the usual care for early sepsis that most of the subjects would otherwise receive if they were not enrolled in CLOVERS.

Nor does the consent form explain to subjects the specific significant deviations from usual care that will occur for each trial group.

For example, there is no mention of the fact that subjects randomly assigned to the liberal fluids group could remain severely hypotensive (i.e., SBPs between 70 and 90 mmHg and MAPs between 40 and 60 mmHg) for several hours without vasopressors being administered when such blood pressure levels would be far below the level that septic shock patients are commonly allowed to fall to or remain at for hours before vasopressors would be started" (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, p. 8; on the Web at https://www.citizen.org/sites/default/files/2446.pdf).

## Allegedly False Implication in Consent Covers Up Real Dangers

"More troublingly, cursory statements like '(s)ome doctors use medicines to raise blood pressure followed by extra fluids, and others use extra fluids followed by medicines to raise blood pressure;' '(s)ome doctors use a combination of the two;' and 'both fluids through a tube in a vein and vasopressors are commonly used in the care of this condition' misleadingly imply that both experimental management strategies are used commonly in usual care of sepsis, though they clearly are not.

Regarding reasonably foreseeable risks, the CLOVERS sample consent form includes the following key statements that purportedly explain the risks of the research:

> ***Side effects and risks that are possible if you take part in this study***
>
> • Risk of Getting Extra Fluids: Patients in the (liberal fluids) group may get extra fluids through a tube in a vein.
>
> It's possible that this could cause stress on your heart related to extra fluid, breathing difficulties, or increased swelling in your arms and legs" (supra at p. 9). © **{TBC}**

# FDA Warning

**Warning Letter To:** Houston, TX IRB (Part 12)
**Warning Letter Date:** September 24, 2012
**Investigation Period:** Ended on April 25, 2012
**Noncompliance:** IRB Members Repeatedly Failed to Follow Regulations; IRB Eventually Disbanded by FDA Order

* * *

## You Can't Make Me Do It, So There

We resume coverage of the errant Texas IRB this month with yet another FDA finding that, despite how the agency instructed the noncompliant IRB to remedy serious problems, the IRB still had its own approach.

"FDA requested that you submit the handwritten notes themselves [about a controversial IRB meeting] rather than to create a typed version of the [allegedly] lost minutes.

Nonetheless, you submitted a typed version of the 2011 handwritten notes with your letter dated October 19, 2012. As we stated in the Warning Letter, it is inappropriate and an unacceptable practice to recreate meeting minutes.

In your October 8, 2012[,] letter, you described the 'implementation of the new electronic back-up system to capture all data files and documentation thereby to ensure availability of all information relative to the clinical research projects in the future.'

The IRB's response is inadequate because you did not provide documentation (e.g., SOPs, etc.) explaining how minutes and study files will be stored and/or protected to prevent the loss of required documentation in the future.

The IRB's failure to maintain meeting minutes in accordance with 21 CFR 56.115 (a) (2) is a repeat violation. It had also been identified in the last two FDA inspections conducted in 2000 and 2007.

B. In your October 8, 2012[,] letter you explain that, effective September 15, 2012, the IRB implemented a new template identifying the information to be recorded to ensure that the minutes of future IRB meetings are in compliance with 21 CFR 56.115(a)(2).

[Your organization's] RRC [Research Review Committee] Procedure manual *RRC Meeting Forms* states 'Minutes of IRB meetings should include sufficient detail to show:

Item 2.b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.

Item 3. Presence of a quorum throughout the meeting.

Item 4 h. Determinations of conflict of interest, if any'" (FDA Warning Letter, September 16, 2014, p. 7).

## Just Because It's On Paper …

"On November 7, 2012, … [your] RRC failed to follow the newly implemented template submitted to the FDA as a corrective action. The November 7, 2012[,] meeting minutes did not document (1) the confirmed receipt of pertinent materials by all IRB members prior to the meeting, nor (2) the presence of [a] quorum throughout the meeting.

In addition, … (Redacted …) was listed as an IRB member who abstained since he requested the review, but (Redacted …) [IRB member's] conflict of interest was not documented in the meeting minutes.

C. At the conclusion of the regulatory meeting on February 22, 2013, FDA requested all documentation of IRB activities conducted by … [your] RRC since FDA's restrictions were imposed on September 24, 2012.

During the meeting you explained that … RRC received a … study in December 2012, and that you referred the protocol to another IRB. FDA requested that you submit the research protocol reviewed by … RRC and all documentation of IRB activities and decisions regarding this research proposal.

The IRB failed to respond to the FDA request for this information, except for stating that the committee did not meet in October or December 2012" (ibid). © **{TBC}**

## In Court

**Case:** Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 54)
**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

* * *

### Ethics Committees and "Institutional Review Boards" Mandated in 1975

We concluded last month's article with the former high school student's emphasis on the importance of informed consent in human research projects, and the historically crucial role played by the Nuremberg Code in guiding today's human subjects research.

We resume our coverage here with an additional comment from the student regarding the Code that was established after the horrific Nazi medical experiments in World War II. The student said:

> "… The Code set forth one very important requirement of ethical human experimentation, which is at issue in this case. The requirement of voluntary consent of the subjects after being informed of all material information about the experiment.
>
> The Code did not just look backward at the events that gave rise to the Doctors Trial but looked forward to post-war research on human beings.
>
> In 1954, the World Medical Association adopted a resolution on human experimentation based largely on the Nuremberg Code. The resolution contained the basic principle that 'it is the duty of the physician in medical research to protect the life, health, privacy[,] and dignity of the human subject.'
>
> In 1964, after several revisions, the World Medical Assembly in Helsinki adopted this document now known as the Declaration of Helsinki. It was revised again in 1975 to include a requirement for ethical review committees, such as Institutional Review Boards and adopted most recently by the 52nd General Assembly of the World Medical Association in Edinburgh, Scotland in October 2000" ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, pp. 13-14).

### Nazis Weren't the Only Ones; Americans Directed Unethical Experiments Too

"In the fifty years after Nuremberg, outrage over a series of public scandals involving human experiments in the United States has reaffirmed this Nation's commitment to human subject protection.

One occurred at New York's Sloan Kettering Institute for Cancer Research where a researcher working on the immune systems' ability to fight cancer convinced the director of the Jewish Chronic Disease Hospital in Brooklyn to allow him to inject unwitting patients with live cancer cells.

A second was the Willowbrook Study, in which researchers at an institution for mentally disabled children sought to develop a hepatitis vaccine by studying children whom they had deliberately infected with isolated strains of the virus.

It was the third scandal with racial overtones, all too reminiscent of Nazi atrocities, which generated federal action to regulate human subject research. The infamous Tuskegee Syphilis Study, conducted by U.S. Public Health Service physicians, was halted in 1972, nearly 49 years after it began while 200 African-American subjects were allowed to remain untreated despite the availability of therapeutic measures.

In 1973, the Ad Hoc Advisory Panel issued its Final Report of Tuskegee Syphilis Study, concluding that society can no longer afford to leave the balancing of individual rights against scientific progress to the scientific community.

Thereafter, Congress appointed a federal commission to examine the system for protecting human research subjects" (pp. 14-15).

The commission's work eventually led to today's "Common Rule" on the protection of human research subjects. © **{TBC}**

## IRB Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** FDA is accepting comments ***until October 25*** on a new draft guidance titled "Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer."

"This draft guidance provides recommendations for sponsors of investigational new drug applications (INDs) and biologics license applications (BLAs) on the use of pharmacokinetic (PK)-based criteria to ***support the approval of alternative dosing regimens*** for programmed cell death receptor-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) blocking antibodies" (86 Fed. Reg. 47649, August 26).

"These antibodies are usually administered intravenously. ***Sponsors may seek approval of alternative intravenous (IV) dosing regimens that are different from those tested in clinical efficacy and safety trials***. These alternative IV dosing regimens are typically designed to change doses … and/or dosing intervals …. Longer dosing intervals can … ***reduce risks*** … (e.g., [due to possible exposure to] SARS-CoV-2) ***associated with visits to hospitals or infusion centers***" (guidance, August, p. 1; on the Web at https://www.fda.gov/151745/media).

For more information, contact: Brian Booth of FDA at 301-796-1508.

• **Food and Drug Administration.** FDA is accepting comments on a new final guidance titled "Premenopausal Women with Breast Cancer: Developing Drugs for Treatment."

"The guidance is intended to assist stakeholders, including sponsors and ***institutional review boards***, responsible for the development and oversight of clinical trials for breast cancer drugs" (86 Fed. Reg. 33313, June 24).

"Historically, ***premenopausal women have been excluded from some trials*** that have investigated the efficacy of certain drugs that rely upon manipulation of the hormonal axis for the treatment of hormone receptor (HR)-positive breast cancer.

In some cases, separate studies have been conducted to confirm the benefit in this patient population, ***which has resulted in delays in the availability of these therapies for premenopausal women with HR-positive breast cancer*** ….

The inclusion of premenopausal women in breast cancer oncology product development programs ... ***bring safe and effective therapies in a timely manner to this patient population***" (guidance, pp. 1-2; at https://www.fda.gov/media/142638/download).

For more information, contact: Jennifer Gao of FDA at 240-402-4683.

• **National Institutes of Health.** NIH has reminded the research community about the ***NIH requirement for a single IRB*** for multisite studies involving human subjects.

"Per NOT-OD-16-094, NIH applicants proposing multi-site studies involving non-exempt human subjects research are ***expected to provide a plan describing the use of an sIRB*** that will be selected to serve as the ***IRB of record*** for ***all*** study sites.

Applicants for NIH funding using the FORMS-F or later grant application packages are instructed ***not*** to submit a plan describing the use of an sIRB at the time of application submission.

However, applicants required to use an sIRB ***are required to provide the name of the sIRB*** of record during Just-in-Time submission ***before*** an award is issued.

If, in delayed-onset research, an sIRB has not yet been identified, the recipient will provide the name of the sIRB to the funding NIH Institute/Center (IC) prior to initiating the multi-site research study/project.

***Providing the name of the sIRB of record satisfies the NIH sIRB policy requirement for an sIRB plan for NIH grant applicants***" ("Reminder of Guidance on Requirement for NIH Single ***Institutional Review Board*** (IRB) Plan," Notice Number NOT-OD-21-174, August 23; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-174.html).

For more information, contact: NIH via email to SingleIRBPolicy@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.**

- **October 5-7, 2021,** Virtual Conference: **"Hot Topics and Practical Considerations for Protecting Human Research Participants."** Topics include informed consent with vulnerable populations, research integrity, ethics and pediatric research, educating medical professionals in the conduct of human research, ethics in genomic research, and updates on the revised Common Rule. Conference is presented by the Society of Clinical Research Associates (SoCRA). Contact: Conference Registrar, SoCRA, at 800-762-7292, or fax to 215-822-8633, or send an email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.
- **October 18-21 and 25-28, 2021,** Virtual Conference: **"MAGI's Clinical Research vConference -- Fall 2021."** The 70+ sessions include regulatory compliance, rights of patients and study participants, research subject injury and indemnification, data security, and quality and risk management. Contact: Norman Goldfarb via email to ngoldfarb@magiworld.org, or see their Web site at https://www.magiworld.org.
- **November 16, 2021,** Virtual Conference: **"2021 Social, Behavioral, and Educational [SBE] Research Conference."** Topics include data lifestyle review strategies, informed consent developments, communication between IRBs and researchers, research with nontraditional vulnerable subject populations, research in K-12 settings, and confidentiality, privacy, and anonymity in SBE research. Conference hosted by Public Responsibility in Medicine and Research (PRIM&R). Contact: PRIM&R, Suite 720, 20 Park Plaza, Boston, MA 02216 at 617-423-4112, or email to info@primr.org, or see their Web site at www.primr.org.
- **November 16, 2021,** Virtual Workshop: **"2021 Advancing Ethical Research Conference: *Preconference Workshop*."** Topics include introduction to IRB ethics and regulations, IRB Chairs boot camp, and lessons learned from the COVID-19 pandemic for clinical research. Workshop hosted by Public Responsibility in Medicine and Research (PRIM&R). Contact: PRIM&R, Suite 720, 20 Park Plaza, Boston, MA 02216 at 617-423-4112, or fax to 617-423-1185, or send email to info@primr.org, or see their Web site at www.primr.org.
- **November 16-19, 2021,** Virtual Conference: **"2021 Advancing Ethical Research Conference."** Topics include multiple ethics and regulation sessions. Contact: PRIM&R at 617-423-4112.

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.

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