The Newsletter for IRBs & Research Ethics Committees

Human Research Report™

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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# IRBs, Informed Consent, and New Consent Language for Studies

In this leading article we do something we seldom do. We're excerpting key highlights from a recent NIH Notice. We usually don't do this for two reasons. First, many -- if not most -- of our HRR readers are likely to have been apprised already of any IRB-related NIH Notice.

Second, even if an IRB member is unaware of the particular notice, individual researchers not on the IRB may be aware of the Notice and may modify their protocols appropriately anyway before submitting them for IRB review.

However, the NIH Notice in question does warrant our special attention, again for two reasons. First, it addresses a highly significant topic for IRBs; namely, informed consent. Second, there is still time (until September 29) for the research community to respond to this NIH proposal.

In our brief preliminary "heads up" about this proposal in last month's "IRB Compliance Comment Deadlines & Notices" feature, we incorrectly listed the comment deadline as October 1. It is actually September 29.

## Focus Is On Sharing of Research Data

The Notice is titled "Request for Information: Developing Consent Language for Future Use of Data and Biospecimens" [emphasis added].

> "NIH is requesting information from stakeholders on the utility and useability of sample language developed for use in informed consent documents for data and biospecimen sharing ….
>
> Responsible sharing of data and biospecimens derived from human participants relies on robust informed consent practices that uphold the principles of autonomy and trust in biomedical research. Fundamental to these practices are clear and efficient communication strategies for conveying potential risks and benefits of sharing.
>
> NIH has heard from its stakeholders that there is a strong interest in sharing best practices for developing informed consent language to support [data] sharing. To assist in this endeavor, NIH has worked to develop sample language that may be used in informed consents when data and biospecimen

**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 **To Be Continued** in subsequent issues are marked at the end of the article with **{TBC}**.

## Also In This Issue





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sharing may occur, as well as 'points to consider' for investigators and Institutional Review Board[s] (IRB[s]) when using or modifying the language.

NIH is interested in input on 1) the sample consent language [as it appears later in the NIH Notice], 2) the 'points to consider,' and 3) any gaps or additional components that should be included.

NIH is also interested in input on any hurdles or barriers to the voluntary use of the sample language and 'points to consider' by the community.

NIH welcomes input from research investigators, institutional review board members, study participants, professional organizations, associations with a focus on research oversight, and other interested members of the public" (NIH Notice No. NOT-OD-21-131, July 1, p. 2 of 7; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-131.html).

## Informed Consent Changes Are Specific

The "sample language" presented by NIH in its Notice is detailed and frequently contains options, depending on the nature of the research, the study timeframes involved, etc. The following excerpt is a representative example for the initial consent component.

"***Component 1: Introduction - Description***

**Considerations for those responsible for study conduct and oversight:** The Introduction-Description component is meant to provide prospective research participants with an introduction to, and description of[,] the storage and sharing of data and biospecimens in the study.

- If participants may be re-contacted to collect new or replacement data or biospecimens, include language to address re-contacting.
- Those responsible for study conduct and oversight will need to consider the appropriate timeframe for data and biospecimen storage based on their study and anticipated uses. For some, the appropriate timeframe may be indefinite, while others may have a clear, limited timeframe.

**Instructions for those responsible for study conduct and oversight:** See sample language below for the Introduction-Description component. If using the sample language, include the first three paragraphs then choose either Option #1 or Option #2. Replace embedded instructions identified in **[bold, bracketed text]** with specific information pertaining to the study and remove **[Option #1 and #2 text]**" (supra at p. 4).

## NIH Wants Input on Consent Proposals

As can be seen from the excerpt above, the NIH Notice contains quite detailed sample consent language, with various options. This is true for the following sections as well: "Component 2: Voluntary Participation," "Component 3: Discontinuation/Withdrawal," "Component 4: Risks and Benefits," and "Component 5: Commercial Application."

Similarly, NIH has the following specific instructions for IRBs and anyone else wishing to comment upon the agency's proposals for new informed consent language, as follows in part:

"Comments should be submitted electronically by September 29, 2021, using the form at https://osp.od.nih.gov/rfi-comment-informed-consent-sharing/.

You may provide comments to one or all of the topics in the comment boxes. Comments received will be posted at https://osp.od.nih.gov/clinical-research/informed-consent/ without changes after NIH has reviewed all of the comments received. Please do not include any proprietary, classified, confidential, or sensitive information in your response ….

Please direct all inquiries to: NIH Office of Science Policy, OD/Division of Clinical and Healthcare Research Policy, Telephone: 301-496-9838, Email: SciencePolicy@mail.nih.gov" (supra at p. 7). ©

# IRBs, COVID, and Experiments With Drugs and Biologics (#2)

As we introduced in last month's HRR, a new FDA guidance on the ongoing COVID-19 pandemic contains useful information for researchers and IRBs. With emphases on trial design and resultant human subject safety, the new guidance is titled "COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention."

"The guidance primarily focuses on the design, conduct, and statistical considerations of master protocols intended to generate or contribute to substantial evidence of effectiveness and adequate characterization of safety of drugs for the treatment or prevention of COVID-19.

However, the principles in the guidance may also apply to master protocols generating proof of concept or dose-ranging data for drugs to treat or prevent COVID-19" (guidance, May, 2021, p. 3; on the Web at https://www.fda.gov/media/148739/download).

## "Master Protocols" Versus Single-Case Experiments

As we noted last month, "master protocols" are multipart experiments designed to address several issues in different substudies, some of which may be simultaneous with different human subjects at different sites.

Designed primarily to save time overall, master protocols pose special challenges for IRBs. The guidance states in part:

"**A. Guiding Principles**

All sponsors developing drugs to treat or prevent COVID-19 should consider the following guiding principles when determining whether to conduct a master protocol or a stand-alone trial.

• Both master protocols and stand-alone trials have strengths and limitations including the following:

- … master protocols can accelerate drug development by maximizing the amount of information obtained and leveraging infrastructure to increase trial efficiency.
- Potential limitation of master protocols include their complexity, which necessitates a high degree of up-front planning and coordination.
- In contrast, a stand-alone trial may be easier to design and conduct; however, typically, fewer scientific questions can be answered" (guidance, p. 4).

## Both Types of Studies Can Be Included in Same Program

"• Given the different types of data that need to be generated during drug development (e.g., proof of concept, dose-ranging, substantial evidence of effectiveness, safety data)[,] a development program may include both master protocols and stand-alone trials.

- For all trials in the development program, a sponsor should clearly identify objectives to allow for the selection of an appropriate trial design.
- Sponsors should provide justification for the to-be-evaluated dose(s). This justification may require measurement of biological activity in applicable investigational products (e.g., neutralizing antibody titers in convalescent plasma).
- In general, master protocols are not intended for first-in-human investigation.

• Sponsors considering master protocols for the development of COVID-19 drugs should engage FDA early in their planning to determine the appropriateness of such approaches.

**B. Trial Design and Conduct Consideration**

Master protocol sponsors evaluating drugs to treat or prevent COVID-19 should consider the following:

• A master protocol should include an appropriate randomized comparator arm. In the COVID-19 setting, a high potential exists for confounding when comparisons are made to participants who were not concurrently randomized because of changes over time such as changes in the standard of care including background treatments and supportive care, circulating SARS-CoV-2, availability of health care resources, or the distribution of enrollment across trial sites and regions" (supra at pp. 4-5). © {TBC}

# IRBs and Cancer Trial Subjects' Eligibility

As we noted briefly last month in our "IRB Compliance Comment Deadlines & Notices" feature, FDA has issued a new guidance on a topic of constant relevance for IRBs; namely appropriate eligibility standards for human subjects.

This particular guidance is titled "Cancer Clinical Trial Eligibility Criteria: Approach to Available Therapy in Non-Curative Settings." A major focus of this guidance is on informed consent factors.

> "For the purpose of this draft guidance, non-curative is defined as circumstances where there is extremely low likelihood for cure or for prolonged and/or near normal survival with available therapies (i.e., hematologic malignancies or solid tumors that are unresectable, locally advanced, or metastatic cancer with unfavorable long-term survival).
>
> For clinical trials of products regulated under part 312 (21 CFR part 312), FDA must determine that study subjects are not exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42(b)(1)(i) and (b)(2)(i) to allow such trials to proceed" (86 Fed. Reg. 33711, June 25).

## Eligibility Includes Very Little or No Hope of a Cure

> "Therefore, eligibility criteria should generally require that patients have received available therapy(ies) that offer the potential for cure in a substantial proportion of patients (e.g., available treatment for pediatric acute lymphoblastic leukemia, classic Hodgkin lymphoma, or testicular cancer) in clinical trials evaluating investigational cancer drugs.
>
> Alternatively, such available therapy should be administered to all patients in the trial, where the investigational drug is added to such therapy (i.e., add-on trial).
>
> However, eligibility criteria in which patients receive an investigational drug(s) in lieu of available therapy is reasonable in the non-curative setting (i.e., when there is no potential for cure or for prolonged/near normal survival) when patients have been provided adequate information to make an informed decision on trial participation.
>
> When planning cancer clinical trials in the non-curative setting, sponsors should consider eligibility criteria as it pertains to available therapy.
>
> FDA encourages sponsors to discuss their drug development plan with FDA early in development, including their approach to available therapy when developing eligibility criteria.
>
> In certain circumstances, FDA may request a specific approach for drug development. When designing cancer clinical trials, the following should be considered in the non-curative setting:
>
> • Expansion of eligibility criteria such that, with appropriate informed consent, patients may be eligible for inclusion in trials of investigational drugs, including first-in-human trials, regardless of whether they have received available therapy in the non-curative setting.
>
> In addition to the elements of informed consent required by 21 CFR part 50.25, including 'a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject,' the informed consent should clearly state that other treatment options known to confer clinical benefit exist, and should include discussion of possible benefits, risks, and uncertainties associated with the drug.[4]
>
> (FN #4: For additional information on informed consent, see 21 CFR part 50 and the draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Sheet* (July 2014) ….)
>
> • Evaluation of patients who have received available therapy(ies) and patients who have not in separate cohorts, particularly if interpretation of efficacy results requires a homogenous patient population.
>
> Alternatively, analyses of efficacy may be performed in pre-specified subgroup analyses, defined by prior receipt of available therapy(ies)" (guidance, pp. 1-2; on the Web at https://www.fda.gov/media/150244/download). ©

# IRBs and Hospital-Acquired Bacterial Pneumonia (#5)

We continue here with more tips for IRBs and researchers contained in the current final guidance from FDA titled "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment."

These types of risks continue as COVID rages and interest in developing applicable research projects increases.

We resume our coverage by presenting the guidance's concluding remarks on the influence, or lack thereof, of prior antibacterial drug therapy on any proposed new research in the same field.

For IRBs, note that a key factor in this discussion is how to weigh risk-benefit ratios for subjects.

> "Specifically, prior antibacterial drug therapy could obscure true treatment differences between an investigational drug and the control drug, introducing bias toward a finding of no difference between treatment groups (i.e., a bias toward a finding of non-inferiority ….)" (guidance, June, 2020, p. 7); on the Web at https://www.fda.gov/media/79516/download).

## Prompting Subject Enrollment Via "Anticipatory Consent"

"However, excluding patients who have received prior antibacterial drug therapy also could have adverse consequences. Specifically, certain trial sites may decline to participate in the clinical trial because of concerns that trial treatment would not represent standard of care and would place patients at risk.

A pragmatic approach to these concerns is to (1) encourage prompt enrollment procedures (e.g., anticipatory informed consent offered to patients at risk for developing HABP/VABP [hospital acquired bacterial pneumonia/ventilator acquired bacterial pneumonia] so that patients can receive the clinical trial treatment initially, with no need for other antibacterial drug therapy; and (2) allow enrollment of patients who have received no more than 24 hours of therapy before enrollment.

Patients who have objective documentation of clinical failure while receiving any duration of prior antibacterial drug therapy for treatment of HABP/VABP can be enrolled" (supra at pp. 7-8).

## Using Secondary Endpoints As Well

"*9. Efficacy Endpoints*

*a. Primary endpoints*

Sponsors should select one of the following two primary efficacy endpoints for clinical trials:

- A primary endpoint based on survival: all-cause mortality can be evaluated at a fixed time point at any time between day 14 and day 28 ….
- A primary endpoint based on survival and no disease-related complications: all-cause mortality or disease-related complications (e.g., development of empyema [i.e., formation of pus between the lungs and the inner surface of the chest wall], onset of acute respiratory distress syndrome, sepsis syndrome, other complications) can be evaluated at a fixed time point at any time between day 14 and day 28.

Sponsors should discuss with the Agency the disease-related complications before initiating the trial.

In general, the primary efficacy analysis should be based on a comparison of the proportions of patients achieving the primary endpoint at a fixed time point from randomization.

*b. Secondary endpoints*

Secondary endpoints can include the following: (1) an assessment of resolution of signs and symptoms of HABP/VABP at approximately 7 to 14 days after the completion of antibacterial drug therapy, (2) days spent in the hospital, and (3) days spent on mechanical ventilation (for VABP and ventilated-HABP patients).

*10. Trial Procedures and Timing of Assessments*

a. Entry visit

At the entry visit, the protocol should specify the collection of baseline demographics, clinical information, sputum specimen for evaluation and culture, and baseline laboratory tests, as appropriate" (supra at p. 8). © {TBC}

# IRBs and Signature Waivers For Clinical Researchers (#4)

We continue here with more details for IRBs and researchers on how to obtain a "Form FDA 1572" to record a researcher's signature that waives certain FDA requirements.

The relevant FDA guidance covers IRB- and researcher-related requirements for domestic U.S. studies and those conducted in other countries.

We present here an excerpt from an earlier version of the same guidance that describes relevant IRB and researcher steps in a Q&A format. This Q&A #12 was referenced in the more current guidance on this same topic, as follows:

"12. For foreign clinical studies conducted under an IND, how can an investigator sign the 1572 when the investigator knows he/she cannot commit to all of the requirements on the form, specifically IRB membership (21 CFR 56. 107)?" ("Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions -- Statement of Investigator (Form FDA 1572), May, 2010, p. 7; on the Web at https://www.fda.gov/media/78830/download).

## Respective Roles of IRBs and IECs

"IRB review and approval is required before a clinical study can be initiated under an IND (21 CFR 56.103(a)). FDA may waive any of the IRB requirements for specific research activities or for classes of research activities otherwise covered by the IRB regulations (21 CFR 56.105), but FDA uses the waiver provision only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable.

The most common circumstance for which FDA receives a waiver request is when a sponsor wishes to conduct a foreign clinical study under an IND. In this case typically an Independent Ethics Committee (IEC) that operates in accordance with Good Clinical Practice (GCP) is utilized instead of a U.S. IRB.

Although its membership and functions for assuring human subject protection are comparable to an IRB, an IEC may not meet all of the IRB requirements contained in 21 CFR Part 56" (supra at pp. 7-8). © {TBC}

# IRBs and Interactions With Acid-Reducing Agents (#3)

As we described in our June HRR, gastric experiments that may be confounded with commonly available remedies pose special challenges for the IRBs that review them. The complications occur in certain drug studies and are presented by over-the-counter acid-reducing agents, or ARAs.

The FDA guidance that contains recommendations for relevant IRBs and researchers is titled "Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications."

We resume our coverage with more FDA recommendations on study design issues that can affect study outcomes and justify (or nullify) the justification for human subject participation.

"• **Dose:** To characterize the worst-case scenario, the sponsor should select the maximum recommended dose of an ARA. The maximum dose of an investigational drug that is intended for therapeutic use is recommended since it is more susceptible to gastric pH-depended DDI [drug-drug interaction] effects.

The sponsor should provide a justification if an alternative dose or dosing regimen is proposed" (guidance, November, 2020, p. 6; on the Web at https://www.fda.gov/media/144026/download).

## Dose Frequency Matters Too

"• **Dosing frequency of investigational drug:** Single-dose administration of the investigational drug is acceptable, unless: (1) there is a change in drug absorption after multiple doses; or (2) the study has to be conducted in patients [sic], and single-dose administration is not beneficial to patients who need continuous treatment.

• **Food intake:** If an investigational drug is intended to be taken in the fasted state, the study should be conducted under fasted conditions. If the investigational drug is intended to be taken without regard to food, the study [still] should be conducted under fasted conditions as it is likely to represent the worst-case scenario" (supra at p. 6). © {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 (#8)

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

We resume with SACHRP's argument that IRBs can be "too safe" as they try to balance compensation for human research subjects with ethical concerns over "undue influence." The committee discusses several reasons why this is so.

"*First*, failure to provide adequate incentives can have a detrimental effect on research and research participants (note that the same is true for inadequate reimbursement and compensation payments).

For example, it may lead to difficulty reaching enrollment targets necessary to answer the scientific questions of interest. Under-enrollment [sic] risks wasting resources and exposing participants to risks and burdens without adequate social value, which are both important ethical considerations.

Moreover, higher incentive payments may help encourage a wider variety of participants to enroll, helping to avoid unjust imposition of risks and burdens on economically vulnerable populations.

These considerations suggest that reducing incentive payment to address concerns about undue influence is not necessarily ethically preferable and may be inappropriately one-sided.

*Second*, it is important to recognize that although the limited available empirical evidence about the effects of payment on research participants is inconclusive, it suggests that payment may not in fact blind participants to risk or impair their comprehension, but rather may increase their levels of caution and perception of risk ....

Finally, it is important to note that IRBs should not assume that incentive payments are likely to compromise participants' decision-making simply because the population of potential participants is economically disadvantaged.

If IRBs bar high incentives out of concern that they will encourage enrollment by individuals of lower socioeconomic status, they should be aware that such individuals may still be encouraged by lower payments -- and in fact may be the only participants so encouraged, leading to justice concerns" (from SACHRP letter to HHS Secretary Azar, September 30, 2019, p. 8; on the Web at https://www.hhs.gov/ohrp/September-30-2019-letter-hhs-secretary.html).

## IRBs Should Not Become "Paternalistic"

"In that case, participant protection has not been increased. Instead, some potential participants may have been discouraged from enrollment, and those who enroll may have been disadvantaged, as the result of unfairly paternalistic overprotection by a well-meaning but mistaken IRB.

The better approach is to acknowledge that, in addition to the role IRBs play in minimizing undue influence by refusing to approve research that would unreasonably contravene participant interests, IRBs must also protect and promote autonomous decision-making by prospective participants through their oversight of informed consent disclosures and the consent process.

To help any potential participant avoid an impulsive or superficial decision that fails to fully consider or understand the risks and benefits of study participation, IRBs should encourage investigators to adopt approaches that will support high-quality decision-making ... such as:

- Setting aside sufficient time for knowledgeable study staff to review the entire consent form with potential participants and answer any questions, rather than permitting a passive consent process in which potential participants are expected to review materials on their own" (ibid). © {TBC}

# OHRP Investigation of IRBs and Researchers

**Project Title:** Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) Trial - ***Article #9***
**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.

* * *

## Even Fixing Informed Consent Would Not Be Enough to Save Study

We resume here with more of Public Citizen's arguments that the CLOVERS study employed woefully inadequate informed consent language and procedures. In fact, Public Citizen alleged, these inadequacies were significant enough to threaten injury and even death for the subjects.

"However, simply revising the consent form to address these deficiencies would not be sufficient to address the serious regulatory and ethical lapses related to CLOVERS protocol's fundamentally flawed design and to salvage the trial .... [The] CLOVERS sample consent includes the following pertinent statements scattered across various sections:

***What is the purpose of this study?***

You are invited to take part in a research study of different ways to use 'intravenous fluids' (fluids given through a small tube placed in your vein) and 'vasopressors' (medicines used to raise blood pressure) to treat 'sepsis,' (a serious infection) ….

We do not know which approach is better in this situation: a) starting medicines to raise blood pressure first and then giving more fluids (if needed), or b) giving a larger amount of fluids first and then giving medicines to raise blood pressure if needed" (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. 7; on the Web at https://www.citizen.org/sites/default/files/2446.pdf).

## Respective Roles of Treatment And Research Physicians

"Right now, the choice of approach is left to the doctors. **Some doctors use medicines to raise blood pressure followed by extra fluids, and others use extra fluids followed by medicines to raise blood pressure. Some doctors use a combination of the two** (emphasis added [by Public Citizen]).

This treatment part of the study will last for 24 hours, and then we will follow you until you go back to where you live. We want to find out whether one of these approaches compared to the other can improve a patient's chances of survival ....

***What will happen and how long will you be in the study?***

Before entering the study, you received an amount of fluids through a tube placed in your vein.

After getting these fluids you will be put into one of the two study groups (see below). You will be in that group for 24 hours. After 24 hours, your doctor will decide how the medicine to raise blood pressure and fluids will be given (if they are still needed).

All other treatments, medicines (such as antibiotics), and procedures commonly used for this condition are allowed in this study based on the judgment of your doctors.

***During the study:*** ...

The research team will inform your doctors about you being in this study. You will receive all other medications (e.g. antibiotics) and treatments that your doctors decide you need. The study team and your doctors and nurses will work together to give you intravenous fluids and medicines to raise your blood pressure based on the treatment protocol that you are assigned to and based on your needs …." (supra at p. 8). © **{TBC}**

# FDA Warning

**Warning Letter To:** Houston, TX IRB (Part 11)
**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

* * *

## IRB Members Lack Necessary Credentials

We continue this month with more of FDA's findings on the multiple failures of this investigated IRB. We resume with the FDA's conclusions about the expertise of the individual IRB members and their ability to appropriately review applicable research protocols.

"Because an IRB must be sufficiently qualified through experience and expertise to review specific research activities, an IRB must retain the necessary expertise to effectively review each protocol it receives.

According to the IRB records, [your] … RRC [Research Review Committee, aka IRB] reviews clinical investigations involving medical devices for adult and pediatric use, as well as biological products for adult use.

However, IRB records indicate that the IRB lacked the professional competence necessary to review these studies and determine whether they met the criteria for approval under 21 CFR 56.111, including whether risks to subjects were 'reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.'

Your letter dated October 8, 2012[,] explains that … [your] RRC does not have a medical doctor as an active, regular voting member of the committee, but the committee has access to a core group of medical advisors that provides expertise and input for any and all clinical research studies the committee encounters.

During the regulatory meeting held on February 22, 2013[,] and in your letter dated March 18, 2013, you stated that … [your] RRC is exploring the addition of licensed medical professionals as active members and the interview process for this activity is underway.

To date, the updated IRB membership rosters do not indicate that a licensed medical professional has been added as an active IRB voting member; however, … [the] RRC has advised us that the IRB has added two medical doctors to the IRB's consultant/medical advisor group.

Ad hoc consultants are not IRB members -- they assist in the review process but because they are not IRB members, they are not permitted to vote. They do not contribute sustained experience and medical expertise to the lRB membership. The decision of an IRB must represent the judgment of the members of the IRB ....

[Your] RRC's repeated failure to retain the professional competence necessary among active voting members adversely affects the rights and welfare of the human subjects in clinical investigation reviewed by the IRB" (FDA Warning Letter, Sept. 16, 2014, p. 5).

## IRB's Promises Do Not Yield Results

"As a result, the IRB's corrective actions are inadequate because you have not resolved the lack of professional competence among the active voting IRB members necessary to completely and adequately review research activities.

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

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

You explained to the FDA investigator that, due to a computer crash, all minutes and data for 2011 were lost. During the September 27, 2012[,] telephone conversation with an FDA representative, you offered to recreate the meeting minutes from the IRB's handwritten notes of the 2011 meeting minutes" (ibid). © **{TBC}**

## In Court

**Case:** Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 53)
**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

* * *

### Modern Human Research Informed Consent Has World War II Origins

In the Court's detailed discussion about the importance of adequate informed consent, it continued to use the findings of the World War II Nuremberg trials as its focus.

We resume here where the Court described further the components of a human subject's "understanding and enlightened decision" on whether or not to participate in an experiment.

> "This latter element requires that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.
>
> [HRR: And here we've been thinking all this time that females can be research subjects too.]
>
> The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment.
>
> It is personal duty and responsibility, which may not be delegated to another with impunity.
>
> 2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study[,] and not random and unnecessary in nature.
>
> 3. The experiment should be so designed and based on the results of animal experimentation …" ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, pp. 12-13).

### All Human Subjects Must Have Right to "Opt Out" of Experiment

> "4. The experiment should be conducted so as to avoid all unnecessary physical and mental suffering and injury.
>
> 5. No experiment should be conducted where there is a priori reason to believe that death or disabling injury will occur ….
>
> 6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiments.
>
> 7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
>
> 8. The experiment should be conducted only by scientifically qualified persons ….
>
> 9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end ….
>
> 10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill[,] and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.
>
> (See copy reprinted at http://www.ushmm.org/research/doctors/codeptx.htm.)
>
> These ten points constitute what is now known as the Nuremberg Code. They were an articulation of what these United States judges believed were the fundamental rights of every human being" (supra at p. 13). © {TBC}

# IRB Compliance Comment Deadlines & Notices

• **Agency for Healthcare Research and Quality.** AHRQ has updated its policy on including certain populations in funded studies, and will use the new policy in making decisions on which applications to fund.

"This revised Notice replaces NOT-HS-03-010 …. The purpose of this policy is to ensure that ***all individuals are included in health services research*** in a manner appropriate to the specific question under study ***so*** that the knowledge gained from AHRQ-funded research is ***equally applicable to all populations*** ….

AHRQ will include in its definition of priority populations those groups identified in Section 2(a) of Executive Order 13985 as members of underserved communities: Black, Latino, and Indigenous and Native American persons, Asian Americans and Pacific Islanders[,] and other persons of color; members of religious minorities; lesbian, gay, bisexual, transgender, and queer (LGBTQ+) persons; persons with disabilities; persons who live in rural areas; and persons otherwise adversely affected by persistent poverty or inequality ….

The ***policy applies to all*** grant applications, solicitations for research contracts, and AHRQ intramural studies" ("AHRQ Policy on the Inclusion of Priority Populations in Research," NIH Notice Number NOT-HS-21-015, May 18; on the Web at https://grants.nih.gov/grants/guide/notice-files/NOT-HS-21-015.html).

For more information, contact: Brenda Harding by email to Brenda.harding@ahrq.hhs.gov.

• **Food and Drug Administration.** Comments are due ***by September 27*** on a draft FDA guidance titled "Rabies: Developing Monoclonal Antibody Cocktails for the Passive Immunization Component of Post-Exposure Prophylaxis."

***IRBs*** and researchers involved in rabies research will find this new guidance to be useful in assessing the adequacy and safety of possible study designs.

"The purpose of this draft is to ***help sponsors*** in the development of anti-rabies virus monoclonal antibody (mAb) cocktails as an alternative to anti-rabies virus immunoglobulin (RIG) as the passive immunization component of post-exposure prophylaxes (PEP) for the prevention of rabies when given immediately after contact with a rabid or possibly rabid animal" (86 Fed. Reg. 40 852, July 29).

For more information, contact: Stephanie Troy of FDA's Center for Drug Evaluation and Research at 240-402-4656.

• **Food and Drug Administration.** A virtual workshop will be offered ***on September 27*** that is titled "Considerations for Progressive Multifocal Leukoencephalopathy [PML] Clinical Trial Designs." PML is a rare, often fatal viral disease that:

"… affects patients with immunosuppressive conditions and those treated with immunomodulatory agents. ***No products are approved for the treatment of PMI,*** and no therapeutic development pathway is established for PML.

FDA seeks to discuss scientific and ***regulatory challenges*** associated with designing clinical trials evaluating PML treatments …." (86 Fed. Reg. 33313, June 24).

For more information, contact: Lori Benner of FDA's CDER at 301-796-1300.

• **Office for Human Research Protections.** OHRP is requesting comments ***until September 27*** on its submission to the Office of Management and Budget (OMB) for a new approval of OHRP's requirement that:

"… ***Institutional Review Board records be submitted when an IRB or its institution request an HHS consultation process***, for proposed research involving, respectively: (1) Pregnant women, human fetuses[,] and neonates; (2) prisoners; or, (3) children, as subjects that are not otherwise approval [sic] by an IRB.

The Office of the Assistant Secretary for Health, on behalf of the Secretary of HHS, may determine that such research can be conducted or supported by HHS after consulting with experts and allowing for public review of, and comment on, the proposed research" (86 Fed. Reg. 40860, July 29).

For more information, contact: Sherrette A. Funn at 202-795-7714 or send email to Sherrette.Funn@hhs.gov. ©

# IRB Compliance Conferences & Courses

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

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

• **September 8-10, 2021,** Virtual Conference: **"22nd Annual Human Subject Protection Conference -- Bioethics, Citizen Science, & Human Subject Protection: Waiting on the World to Change."** Topics include ethics of engaging patients in research, conducting reviews on emergent health issues/outbreaks, considerations of a research participant and caregiver, and regulatory updates on the Common Rule. Conference cosponsored by the University of Cincinnati, Cincinnati Children's Hospital, the Office of Research Integrity, Advarra, and others. Contact: Conference Coordinator at 513-761-4100, or send email to hspconference@advarra.com.

• **September 22-25, 2021,** Virtual Conference: **"2021 Annual SoCRA Conference."** The topics include recent changes to the Common Rule on protecting human research subjects, FDA audit findings and how to avoid common clinical trial pitfalls, adverse event monitoring and reporting, FDA guidelines for e-consent, and best practices for IRBs. Conference is hosted by the Society of Clinical Research Associates (SoCRA). Contact: Conference Registrar, SoCRA, at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org.

• **September 24, 2021,** Virtual Workshop: **"Review of Third-Party Research Risk: Is There a Role for IRBs?"** Topics include rights and protections of third parties, third party risks in clinical research, limiting non-consenting third parties to reasonable research risks, public risk perceptions, and possible role of IRBs in reviewing third-party research risks. Conference is hosted by the federal Office for Human Research Protections (OHRP). Contact: Yvonne Lau, Director, Division of Education & Development, OHRP, at 240-453-8236, or send email to Yvonne.Lau@hhs.gov.

• **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. ©

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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