Celebrating our 35th year published every month - Now emailed!

Human Research Report™

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

Volume 35, No. 11 ISSN 0885-0615 November, 2020

IRBs, COVID, and New Exception to Requirement for "Single IRB Review"

COVID has caused yet another change to federal policies on the protection of human subjects. This change, of immediate import for IRBs and researchers alike, involves the relatively recent requirement for the use of only one IRB in many multisite human research experiments.

> "To ensure that institutions conducting cooperative research are able to take advantage of the most appropriate IRB review structure, the Office for Human Research Protections (OHRP) in the Office of the Assistant Secretary for Health of the Department of Health and Human Services has determined that, for studies that are conducted or supported by HHS and subject to the 2018 Requirements [i.e., the massive changes to the traditional Common Rule for the protection of human subjects], and for purposes of 45 CFR 46.114 (b)(2)(ii), an exception to the requirements to use a single IRB is appropriate for the following category: Cooperative research ...." (email alert from OHRP, October 8).

When Use of a Single IRB Is Not Appropriate

We now present the detailed related document on the OHRP Web site titled "October 8, 2020: Exception to the Single IRB Review Requirements for Certain HHS-Conducted or -Supported Cooperative Research Activities Subject to the 2018 Requirements During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency."

> "Cooperative research projects are those projects covered by the 2018 Requirements that involve more than one institution (45 CFR §46.114(a)). The compliance date for this requirement was January 20, 2020.
>
> The 2018 Requirements provide that the Federal department or agency conducting or supporting cooperative research may except the research from the single IRB mandate. To do so, the Federal department or agency must both determine and document that using a single IRB is not appropriate for the particular context (45 CFR 46.114(b)(2)(ii)).
>
> Due to the public health emergency posed by COVID-19, the Office for Human Research Protections (OHRP) is exercising its discretion, as specifically permitted by 45 CFR §46.114(b)(2), to issue this exception to apply in

NOTE #1: Quoted materials in this newsletter appear exactly as originally published in source documents, including any misspellings, grammatical errors, missing words, etc. However, we will on occasion insert words in brackets [ ] to make the material easier to read, to edit text or formatting, or to add an editorial comment.

NOTE #2: Emphases are added to articles by HRR by underlining or adding ***bold/italics*** to selected text, unless stated otherwise.

NOTE #3: Articles **T**o **B**e **C**ontinued **{TBC}** in subsequent issues are marked at the end with **{TBC}**.

Also In This Issue

Published monthly by The Deem Corporation, P.O. Box 451117, Omaha, NE 68145. Editor and Publisher: Dennis M. Maloney, Ph.D.

the conditions outlined herein, on the basis that using a single IRB is not appropriate for this research context.

We believe that this determination of exception is a statement of agency policy that is not subject to the notice and comment requirements of the Administrative Procedure Act (APA) (5 U.S.C. § 553(b)(A))" (on the Web at https://www.hhs.gov/ohrp/regulations-and-policy/single-irb-exception-determinations/october-2020-exception-determination/index.html).

Comments Not Sought Due to Emergency

"For the same reasons explained above, OHRP additionally finds that, even if this determination of exception were subject to the public participation provisions of the APA, prior notice and comment is impracticable and contrary to the public interest, and there is good cause to issue this determination of exception without prior public comment and without a delayed effective date (5 U.S.C. §53(b)(B) & (d)(3)).

This exception is applicable as of October 8, 2020.

II. Determination of Exception

To ensure that institutions conducting cooperative research are able to take advantage of the most appropriate IRB review structure, OHRP has determined that, for studies that are conducted or supported by HHS and subject to the 2018 Requirements, and for purposes of 45 CFR 46.114(b) (2)(ii), an exception to the requirement to use a single IRB is appropriate for the following category:

Cooperative research:

- that is ongoing or initially reviewed by the IRB during the Coronavirus Disease 2019 (COVID-19) public health emergency, as declared by the Secretary of Health and Human Services at https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx;
- where reliance on a single IRB would not be practical; and
- for which the HHS division supporting or conducting the research approves of the use of this exception.

This exception applies for the duration of the research.

OHRP has made this exception determination due to concerns regarding the application of the single IRB requirement to cooperative research subject to the 2018 Requirements when this research is initially reviewed or ongoing during the COVID-19 public health emergency" (ibid).

When Single IRB Reviews Do Not Fit

"The COVID-19 public health emergency has created unprecedented burdens and disruption to the research enterprise, while at the same time requiring urgent research responses that necessitate flexible approaches to oversight in order to provide vital information and to allow other research to continue where possible.

This exception represents an effort to prioritize the health and safety of both research subjects and investigators, and provides flexibility to institutions in seeking IRB review due to the unique challenges created by the COVID-19 outbreak.

Scenarios for which OHRP anticipates it may not be practical to rely on use of a single IRB for multi-site, cooperative research trials during the ongoing COVID-19 pandemic include (but are not limited to):

- Trials for which timely administration of an intervention for the rapidly emerging COVID-19 outbreak is paramount, but:
  - research sites cannot be identified in advance due to the unpredictable nature of the exact location of the outbreak and patients cannot be moved to an existing trial site or to a newly established site without further increasing public health exposure risks; or
  - institutions lacking existing reliance agreements, especially those in underserved or under-resourced areas, may face delays in starting the trial and in administration of the intervention while reliance agreements are negotiated.
- Trials leveraging existing federally-supported trial networks to maximize access to appropriate patients, but where each network is operating under a different single IRB of

record and negotiating reliance agreements between the networks and single IRBs could reduce the ability of qualified sites to access appropriate patients at the correct stage of disease.

• Trials in which a federal research agency wishes to participate as a research site with non-federal (but federally-supported) sites but is legally prohibited from agreeing to certain terms in reliance agreements required by the non-federal sites.

• A cooperative research study supporting the response to the COVID-19 outbreak in which the lead site is engaged in administration of an intervention and in addition is receiving study-wide identifiable samples and/or data for the purposes of determining risk factors linked to COVID-19 disease susceptibility, severity, outcome, or for developing potential diagnostics or therapeutics" (ibid).

Complications for IRB Agreements

"The sites that would be engaged in the research may include institutions that do not have standing reliance agreements within a research network and establishing new reliance agreements would cause unacceptable delays as well as result in a lost opportunity to collect critical COVID-19 samples and data.

• Trials in which the lead site or IRB is unable to provide oversight due to disruption in operations caused by the COVID-19 public health emergency, but other sites can continue, and selecting another site as the IRB of record would require renegotiation of reliance agreements with a new IRB of record, and the study would otherwise be required to halt until such agreements were in place.

Note that this exception determination is only made for purposes of section 46.114(b)(2)(ii) - namely, for determining whether certain cooperative research may be excepted from the single IRB mandate.

This exception determination does not prevent, nor should it be viewed as discouraging, the voluntary use of a single IRB in cooperative research subject to the 2018 Requirements that would fall into the above category.

HHS fully expects use of [a] single IRB where possible even during the COVID-19 public health emergency. Approved use of the flexibilities provided under this exception do not change any other obligations under the 2018 Requirements" (ibid). ©

IRBs and Infection Research With Children as Subjects (#1)

IRBs continue to face special challenges when reviewing protocols that involve children as the research subjects. One area that recently received attention from FDA is the participation of children in infection research.

The relevant new draft guidance is titled "Development of Anti-Infective Drug Products for the Pediatric Population." As the following summary shows, this new guidance covers several topics of major importance for IRB reviews of any applicable studies.

> "The guidance addresses initiation of pediatric clinical studies, enrollment strategies, extrapolation of efficacy, and other considerations to help facilitate pediatric anti-infective drug product development" (85 Fed. Reg. 39193, June 30).

Safety Data From Adult Studies Can Help

The five-page guidance describes specific attributes of clinical pediatric studies such as human subject protection topics like:

> "• Safety data:
>
> - In general, safety data should be collected in all pediatric age ranges for which the drug product will be indicated, using the intended dose and duration of the drug product.
>
> - Safety data from adult clinical studies can provide supportive information and identify adverse events of interest for evaluation in pediatric studies.
>
> - The size of the recommended pediatric safety database of a drug product depends on several factors, such as the prevalence of the disease, adverse event profile of the drug product or drug class, and expected use of the drug product in the pediatric population .... [and] ...
>
> - For pediatric studies that are intended mainly to evaluate safety and/or pharmacokinetics, there can be some flexibility in the inclusion and exclusion criteria to identify pediatric patients for enrollment, such as duration of prior antibacterial therapy and choice of comparators based on standard of care at the enrolling site" (guidance, page 4; on the Web at https://www.fda.gov/media/139586/download). © {TBC}

IRBs and Parental Permission In Research With Children (#1)

IRBs have traditionally faced a number of challenges when reviewing protocols that involve the participation of children as the research subjects.

Both HHS regulations, and the separate ones for FDA-regulated products, contain specific directions for how informed consent is to be sought in such studies.

For example, an IRB may approve research that falls into three categories, and HHS must convene a panel of experts to review any proposed study that does not fit any of the three allowable conditions.

HHS is currently reviewing new recommendations for IRBs and researchers on particular aspects of research involving children. These recommendations were submitted to HHS in late 2018 and are still under review at HHS.

The recommendations, as usual, were developed by the Secretary's Advisory Committee on Human Research Protections (SACHRP).

We expect that these SACHRP recommendations, also as usual, may well lead to new IRB regulations and/or federal policies.

What Does a "Reasonably Available" Parent Mean for Parental Permission?

"Once the IRB determines which regulatory provision applies to the research under review, reference is then made to [CFR Part 45] 46.408 and/or [CFR Part 21] 50.55 which sets out the requirements relating to the permission of the parent or guardian.

The permission of one parent is sufficient for the first two [of the three traditional] categories (46.404, 46.405, 50.51,50.52).

For research falling under 46.406/50.53, if permission is to be obtained from parents, permission must be obtained from both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Both IRBs and investigators have expressed confusion about how the term 'reasonably available' should be applied and interpreted.

We start with the premise that determining whether one parent is reasonably available necessarily begins from the assumption that both parents are known and legally competent, and both have legal responsibility for the care and custody of the child.

There exists a broad, varied[,] and inconsistent spectrum of opinion as to what may be considered an appropriate determination [of] whether a parent is or is not reasonably available.

Generally, IRBs do not review the circumstances of whether a second parent is reasonably available for each enrolled subject; this is a task for the investigator.

The IRB determines the requirement for parental permission at the time of IRB review of the research, based on the regulatory category that is most appropriate to the nature of the research under review and with regard to the entire population of prospective subjects.

It is not until the investigator meets the parent(s) and child and discusses the particulars of the research and enrollment that information about the availability of both parents becomes apparent" ("Attachment D - Parental Permission in Research Involving Children," October 17, 2018; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-d-november-13-2018/indes.html). [sic]

When Parental "Availability" Is a Problem

"While the IRB may certainly be consulted by investigators for guidance on a particular situation, it is ultimately the responsibility of the investigator to adequately assess, document[,] and decide whether a parent is not reasonably available given the specific facts and circumstances of each situation, including the level of that second parent's participation in the life of the child.

When the IRB requires that permission be provided by two parents, and both parents provide permission, there is no issue. The problem arises when both parents are known and competent and have legal responsibility for the child but the permission of the second parent is not obtainable.

Here, the absence of permission by a second parent could be because the second parent:

1. does not want to participate in the informed consent process;
2. is not reasonably available; or
3. is reasonably available to provide permission for the child's participation but is not reasonably available in terms of providing a signature" (ibid). © {TBC}

IRBs and Developing Drugs and Biologics During COVID-19 (#5)

In concluding last month's article on highlights of FDA's guidance titled "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention," we presented recommendations on clinical trial endpoints to use when designing relevant human subject studies. We refer applicable IRBs and researchers to pages 9-10 of that guidance for additional endpoint selection choices.

For the present article, we move on to the draft guidance's section addressing a topic of equally immediate use to IRBs; namely, recommendations on ways to ensure the safety of human subjects, as follows:

"**D. Safety Considerations**

Sponsors of drugs to treat or prevent COVID-19 should consider the following:

• It is important to include a broad population of subjects in adequate and well-controlled clinical trials to generate a safety database that will best inform the safe use of the drug" (guidance, May, p. 10; on the Web at https://www.fda.gov/media/137926/download).

Recommendations on Several Safety Factors for Human Research Subjects

"• The size and composition of the safety database needed to support an indication for COVID-19 depends on factors such as the proposed population, the treatment effect, the drug's toxicity, and the extent of the prior clinical experience with the drug (and possibly with related drugs).

• Sponsors may provide a standardized toxicity grading scale for clinical trials in patients with severe COVID-19 or patients with serious comorbidities. Examples of toxicity grading scales include those published by the National Institutes of Health's Division of AIDs[25] and the National Cancer Institute (NCI).[26]

[FN #25: See the National Institutes of Health's Division of AIDS Adverse Event Grading Tables, available at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

FN #26: See the National Cancer Institute's Common Terminology Criteria for Adverse Events, available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.]

• Sponsors should address the potential for drug-drug interactions that could increase the risk for toxicities (caused by increased exposures of the drug or the drug that it interacts with) and propose mitigation strategies.

• Safety assessments (e.g., vital signs, laboratory studies, electrocardiograms) should be performed on a schedule commensurate with severity of illness and the identified potential risk of the study drug.

• Sponsors should conduct safety reporting as outlined in FDA regulations[27] and relevant guidance.[28]

[FN #27: See 21 CFR 312.32.

FN #28: See the guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012). In addition, FDA has proposed relevant recommendations in the draft guidance for industry *Safety Assessment for IND Safety Reporting* ....]" (supra at p.11).

Subject Safety and Use of Statistics

"**E. Statistical Considerations**

Sponsors of drugs to treat or prevent COVID-19 should consider the following statistical considerations:

• The primary efficacy analysis should be conducted in an intention-to-treat population, defined as all randomized subjects.

• The primary efficacy analysis should be prespecified in the protocol.

• To the extent possible, sponsors should justify their assumptions in sample size calculations. The sample size should be large enough to provide a reliable answer to the safety and efficacy questions the trial is meant to address ....

• To improve the precision of treatment effect estimation and inference, sponsors should consider adjusting for prespecified prognostic baseline covariates (e.g., baseline severity, comorbidities) in the primary efficacy analysis and should propose methods of covariate adjustment. For example, for a binary endpoint, methods can be used to gain precision in the evaluation of the difference in proportions.[29]

[FN #29: Ge M, Durham LK, Meyer RD, Xie W, and Thomas N, 2011, Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences, *Drug Inf J*, 45:481-493.][sic]" (supra at pages 11-12). © **{TBC}**

IRBs and Reviewing Certain "Live Case Presentations" (#6)

We return now to a topic we last covered in the May issue; namely, the special challenges posed for IRBs and others in studies that include at least some portion of a "live case presentation."

The relevant FDA guidance is titled "Live Case Presentations During Investigational Device Exemption (IDE) Clinical Trials: Guidance for Institutional Review Boards, Industry, Clinical Investigators, and Food and Drug Administration Staff."

We resume where we left off, with more advice from FDA on what kinds of information should be included in an IDE application when a live case presentation is involved.

> "... if live case presentations are anticipated for any part of an investigation at the time an original IDE application is submitted, the plan for the live case presentation should be discussed in the original IDE application" (guidance, July 11, 2019, p. 7; on the Web at https://www.fda.gov/media/88454/download).

Agency Focus Is on Human Subject Factors Such as Informed Consent

> "The following information should be included when requesting approval for a live case presentation either when the original IDE application is submitted, or as a supplement to an IDE application:
>
> • The total number of live case presentations anticipated over the duration of the study;
>
> • A justification for the live case presentation; if more than one live case presentation is requested, provide a justification as to why more than one is necessary;
>
> • The name(s), date(s), and location(s) of the event (if known) where the live case presentation will be broadcast and the investigational site where the procedure will be conducted;
>
> • The name and qualifications of the operator/investigator performing the procedure, or reference to where the information is located if previously submitted or summarized in a different section of the IDE;
>
> • A copy of the informed consent document(s) for the live case presentation to be used at each investigational site;
>
> • A discussion of methods utilized to minimize risks; and
>
> • A discussion of how the live nature of the case will affect the scientific soundness of the study and how the live case data will be addressed in the statistical analysis or otherwise be used to support device approval or clearance.
>
> If it is not anticipated at the time of the original IDE, the live case presentation request should be submitted as a supplement to the original IDE in accordance with 21 CFR 812 .35(a) at least 30 days prior to the planned presentation.
>
> This is because original IDE applications and supplements have a 30-day review period. The supplement may reference any information that was already included and approved in the original IDE.
>
> If a live case presentation is anticipated at the time of the original IDE application, but specifics about the live case presentation are not known at that time, FDA intends to focus its review on the risk analysis, the informed consent, and the impact of live case presentations on the study design and data analysis" (ibid).

Possible Effects on Human Subjects Are Major Concerns

> "FDA also has concerns related to clinical study execution as identified below. FDA therefore recommends that the following additional items be specifically addressed when designing or revising an investigational plan to include live case presentations:
>
> • Live case presentations typically include prior subject selection and may result in unblinding the investigator and subject. The potential for investigator and selection bias should be addressed, as well as how this bias will be minimized;
>
> • Sponsors should include a discussion of how subjects participating in live case presentations will be addressed in the planned endpoint analyses.
>
> For example, sponsors should specify if these subjects will be excluded from the overall effectiveness analysis and reported as a separate cohort.
>
> Sponsors should adjust sample sizes after considering whether subjects should be excluded from primary outcomes analyses ..." (supra at p. 8). © {TBC}

IRBs and Research With Neonates (#3)

With this article we conclude coverage of a young human subject population that poses special challenges for IRBs even beyond those normally presented by children; namely, the population of neonates.

We last presented highlights of the relevant FDA guidance for this area in our November 2019 HRR (p. 4). We will return to this guidance in the future if events permit, but the unusual flurry of regulatory and policy changes caused by COVID means that we must focus on more pressing issues for IRBs than the intricacies of neonatal research.

Therefore, for IRBs and researchers exclusively concerned with this particular population, we recommend the applicable guidance cited below.

However, we note that there are some general IRB issues for this subject population that we have not covered previously (e.g., research subject sampling), and these IRB issues do merit adding below in this concluding article.

An Unusual Human Subject Population

"V. Study Design Considerations

Conventional pharmacokinetic studies that include intensive blood sampling can rarely be undertaken in neonates because of their limited circulating blood volume.

Another consideration is the variability in the study population (e.g., a population undergoing rapid and varying rates of maturation) which makes collection of clinical pharmacology information (e.g. PK [pharmacokinetic], PD [pharmacodynamic], etc.) uniquely challenging.

Hence, it is important to use all available information and innovative approaches when designing a neonatal study. When designing neonatal clinical studies, sponsors should be mindful that modeling and simulation and pharmacologic considerations are often critical for the successful completion of a study ....

The following sections describe considerations for key trial design elements when developing a neonatal study plan.

A. General Approaches to Providing Substantial Evidence of Safety and Effectiveness in Neonates

There are several approaches to providing substantial evidence of safety and effectiveness for drugs for the pediatric population:

• Considering the distinct disease processes seen in the neonatal population, it is expected that pediatric extrapolation of effectiveness from other populations (e.g. adults, older children) would be infrequently used ....

The magnitude of the safety database needed is determined by several factors, including for example, experience with similar drugs in populations of older children, adults, and neonates and the seriousness of the adverse reactions in the adult or pediatric populations" ("General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products," July, 2019, p. 9; on the Web at https://www.fda.gov/media/129532/download).

Required Reliance On Many Data Sources

"• Most drugs developed for use in neonates require adequate and well-controlled studies for the specific neonatal indication. The prospect of a direct benefit to the neonatal study participants would depend on the disease or condition and its severity, the availability of alternative treatments, and the absence of a major or significant safety concern based on data in adults, older children, or animal and in vitro models (if no human data are available) ....

B. Study Population

When conducting clinical pharmacology studies in neonates, the population enrolled should involve neonates that have the disease or condition of interest or, in some cases, neonates who may be at risk for the disease or condition of interest.

To account for variability in age, it may be necessary to evaluate the product across a wide spectrum of PMA [post-menstrual age] and PNA [postnatal age] subgroups of neonates, as long as the indication to be studied is relevant in those subgroups ....

C. Dose Selection

Selection of an appropriate dose range to be studied is critical in deriving rational dosing recommendations for the neonatal population. Investigators should use all existing pharmacokinetic and pharmacodynamic data (from adults, older pediatric patients, etc.) to help determine an initial dose in neonates.

Clinical trial simulations that integrate PK, PD, biomarkers, and disease progression may help make this initial determination ...." (supra at p. 10). ©

Published each month since January, 1986
Web: www.IRBusa.com

HUMAN RESEARCH REPORT™
Emailed to subscribers between the 7th and 11th of each month

IRBs and Research On Prisoners (#6)

We resume here with additional information about an alleged major abuse of prisoners as human research subjects. At the end of our last article on this allegation made by Public Citizen about the company BioCorRx, we presented details from THE NEW REPUBLIC magazine (see June HRR, p. 5).

The entire matter centered on the experimental use of the drug Naltrexone as an implant to combat opioid and alcohol abuse and addiction in the Louisiana prison system. Allegations included alleged failure of informed consent to adequately explain to the prisoners what was done to them.

We resume here with portions of Public Citizen's formal written complaint to the FDA.

> "THE NEW REPUBLIC also reported that 'after the prison was criticized for giving an unapproved drug to a prisoner, the Louisiana Department of Correction discontinued its use of Naltrexone implants in the spring,' although the exact timing of this discontinuation is unclear" ("Company Tested Unapproved Implanted Drug on Louisiana Prisoners in Apparent Illegal Clinical Trial; FDA Must Investigate," November 20, 2019, p. 5; on the Web at https://www.citizen.org/news/company-tested-unapproved-implanted-drug-on-louisiana-prisoners-in-apparent-illegal-clinical-trial-fda-must-investigate/).

Allegations Include Failure to Get IRB Approval for Research

> "The above statements [including those in our June HRR] taken together could not be clearer: BioCorRx and the LDPSC [Louisiana Department of Public Safety and Corrections] initiated a clinical investigation under the rubric of a 'pilot program,' the primary purpose of which was to evaluate the clinical effectiveness and cost-effectiveness of a non-FDA-approved, investigational multimonth sustained-release naltrexone implant, in combination with cognitive behavioral therapy modules and peer support, for management of opioid use and alcohol use disorders in prison inmates.
>
> **Apparent regulatory violations**
>
> In accordance with the requirements of FDA regulations for the protection of human subjects at 21 C.F.R. Parts 50 and 56, any clinical investigation involving an FDA-regulated test article, such as an investigational sustained-release naltrexone implant, must be reviewed and approved by an IRB.
>
> Additionally, the legally effective informed consent of the human subjects of any clinical investigation must be obtained and documented using a written consent document that is approved by the IRB and that embodies all of the elements of informed consent required by 21 CFR §50.25, except in certain limited circumstances that would not have applied to a clinical investigation of a sustained-release naltrexone implant for treatment of opioid and alcohol use disorders" (ibid).

Who Needs an IRB Review Anyway - It'll Probably Just Slow You Down

> "But a review of email correspondence between BioCorRx and the LDPSC from early December 2018 to late April 2019 related to the establishment of their partnership for the pilot program revealed no mention of IRB review and approval of the pilot program.
>
> The email correspondence also included consent forms ... that would typically be used for clinical care and that lacked the elements of legally effective informed consent required under FDA human subjects protection regulations at 21 C.F.R. §50.25 for an FDA-regulated clinical investigation.
>
> Moreover, according to the October 31, 2019, report in THE NEW REPUBLIC, BioCorRx asserted that 'it didn't need to go through (an IRB) because it was not technically conducting a trial,' thus confirming the company's failure to obtain IRB review and approval of the apparent clinical investigation.
>
> As a result, there was no opportunity for an IRB to ensure that the clinical investigation testing the effectiveness of sustained-release naltrexone implants for treatment of opioid and alcohol use disorders in prison inmates satisfied the following FDA regulatory requirements at 21 C.F.R. Parts 50 and 56:
>
> (1) Risks to subjects are minimized: (a) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (b) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes" (supra at pp. 5-6). © {TBC}

FDA Warning

Warning Letter To: Houston, TX IRB (Part 1)
Warning Letter Date: September 24, 2012
Investigation Period: Ended on April 25, 2012
Noncompliance: IRB Members Repeatedly Failed to Follow Regulations

* * *

Agency Investigation Clearly Showed Major Failures By IRB to Follow Regulations

In this first of a series of articles we begin by describing a striking event in the IRB world; namely, the formal disqualification of an IRB by the FDA from ever reviewing a human subjects protocol again.

We begin with FDA's initial description of its investigation and the subsequent intermediate FDA actions and sanctions that spanned a period of several years.

"This letter describes the results of a Food and Drug Administration (FDA) inspection of the Texas ... Research Review Committee [RRC] ... that concluded on April 25, 2012. The FDA investigator conducted the inspection of this Institutional Review Board (IRB) to determine if the IRB's activities and procedures for the protection of human subjects comply with FDA regulations published in Title 21, CODE OF FEDERAL REGULATIONS (CFR), Parts 50 and 56.

The FDA conducted this inspection under its Bioresearch Monitoring Program, which includes inspections designed to review IRB operations relating to clinical studies of FDA regulated products and to ensure that human subjects are protected from undue hazard or risk during the course of clinical studies.

At the end of the inspection a Form FDA 483, Inspectional Observations, was issued and discussed with you. We reviewed the inspection report, the Form FDA 483 and your letter dated May 11, 2012, sent in response to the Form FDA 483.

We have determined that the IRB significantly violated applicable federal regulations governing the operation and responsibilities of IRBs as published under 21 CFR Part 56 (available at http://www.gpoaccess.gov/cfr/index.html).

This letter requests prompt corrective action to address the violations cited and discusses your IRB's written response to the noted violations. The applicable provisions of the CFR are cited for each violation" (Warning, p. 1).

Conflict of Interest Is Conflict of Interest, Even When Conflict Is Denied

"1. The IRB failed to ensure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest. (21 CFR §56.107(e)).

The ... RRC procedures manual, RRC Membership, states that no member of the Committee shall be involved in either the initial or continuing review of an activity in which he or she has a conflicting interest, except to provide information requested by the reviewing body.

The meeting minutes dated January 26, 2012, show that two of the ... [redacted by FDA] committee members, including you as the Chairperson, participated in the initial review and approval of clinical studies sponsored by (hereafter, ... [redacted by FDA]) in which the members had a conflict of interest. Both you and ... [redacted by FDA] voted to approve protocols sponsored by ... [redacted by FDA] even though you had both provided consulting services to ... [redacted by FDA] assisting with writing protocols and informed consent documents, for which payment was requested.

In your letter, you disagree with the observation that ... [redacted by FDA] IRB members had a conflict of interest with the review of the... [redacted by FDA] clinical studies.

You explain that one of the IRB committee members assisted in the initial drafting of the ... [redacted by FDA] clinical study protocols and that consulting services provided to ... [redacted by FDA] by ... [redacted by FDA] and/or ... [redacted by FDA] are not conflicts of interest ....

We disagree with your explanations. The two members in question had a conflicting interest when they participated in the initial review and approval of the protocols and informed consent documents which they assisted in drafting. Conflicting loyalties, whether conscious or not, may influence the IRB's deliberations" (supra at pp. 1-2). © {TBC}

In Court

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 43)
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

* * *

Defense Gives Reasons Why Lawsuit By High School Student Should Be Dismissed

With this article we conclude coverage of the defense's memo to the court claiming that the plaintiff high school student was an "incidental party" and not a "third party beneficiary" to the university's Assurance on protecting human subjects.

Hence, argued the defendants, the girl had no special rights relevant to the case and could not sue over her involvement in the mandatory drug-use research.

We resume here with the defense's explanation, in citing previous court cases, why the student was not in a position to sue. Along with other cases, the defendants cited *Allstate Transportation Company, Inc. v. Southeastern Pennsylvania Transportation Authority* (E.D. Pa. Mar. 27, 2000):

> "... (in holding that the plaintiff was not a third-party beneficiary of a grant agreement between the defendant and the U.S. Department of Transportation in which the defendant promised to comply with federal regulations and Title VI of the Civil Rights Act, the court found 'no specific language within the Grant Agreement ... indicating that (the defendant) may be held liable to third parties in the event of nonperformance'); [and also in the case of] *Minor v. Northville Public Schools*, 605 F.Supp. 1185, 1199 (E.D. Mich. 1985) (in action against school board by teacher for discrimination in violation of Title IX of the Educational Amendments of 1972 based on school board's adoption of an assurance of compliance with federal regulations in order to receive federal funds, holding 'it is beyond peradventure that the execution of the certificate of assurance creates no substantive rights on plaintiff's behalf').
>
> OHSU, by assuring compliance with the DHHS policy regarding research involving human subjects, agreed that if the DHHS were to find any material noncompliance by OHSU with the DHHS policy, its federally-funded research could be terminated or suspended. Assurance Agreement at 1; 45 C.F.R. §46.123" ("Memorandum in Support of Defendants ...," November 4, 2002, Docket Document #20, p. 41).

Defense Sums Up Its Argument On "Third Party Beneficiary"

> "OHSU did *not* agree to potential liability to third parties for noncompliance. The absence of anything in the Assurance Agreement that provides for such third party liability is fatal to plaintiff's claim, and her Fourth Claim for Relief should be dismissed.
>
> **CONCLUSION**
>
> For all the foregoing reasons, plaintiff's Second Amended Complaint should be dismissed in its entirety, without leave to amend, and with prejudice. If this court dismisses only plaintiff's federal claims, this court should exercise its discretion and dismiss plaintiff's supplemental state law claims [as well]. 28 U.S.C. §1367(c)(3); *Bryant v. Adventist Health Systems/West*, 289 F.3d 1162, 1169 (9th Cir. 2002).
>
> In the alternative, this court should strike all allegations in the Complaint that purport to assert the rights or interests of third parties, and strike plaintiff's prayers for punitive damages under her common law tort claims" (supra at pp. 41-42).

The next major action in this case is the high school girl's attempt, as the plaintiff, to get the defendant's "Motion to Dismiss" denied by the court.

> "This case is not about the constitutionality of drug testing high school athletes or whether drug use is a problem in America's schools. It is about whether the defendants designed and conducted an unethical human experiment on plaintiff Beth Wade ('Wade') and other Oregon high school students without obtaining their voluntary consent" ("Plaintiff's Memorandum in Response to Defendants' Motions to Dismiss," December 9, 2002, Docket Document #27, p. 1). © {TBC}

Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** Comments are ***due by November 23*** on the current reporting and record keeping requirements of FDA's program titled "Use of Public Human Genetic Variant Databases to support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics" (85 Fed. Reg. 50801, September 23).

FDA's request to the Office of Management and Budget (OMB) for approval of said procedures represents an extension of OMB's current approval (OMB Control Number 0910-0850). The relevant guidance describes:

> "... how publicly accessible databases of human genetic variants can serve as ***sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships to FDA's regulatory review of both NGS-based tests*** [i.e., tests based on 'next generation sequencing'] and genetic and genomic tests based on other technologies" (85 Fed. Reg. 59802, September 23).

For more information, contact: Ila S. Mizrachi of FDA's Office of Operations at 301-796-7726, or send email to PRAStaff@fda.hhs.gov.

• **Food and Drug Administration.** Comments are ***due by December 1*** on a new draft guidance titled "Bladder Cancer: Developing Drugs and Biologics for Adjuvant Treatment."

This guidance contains information ***for researchers and IRBs*** that is similar in intent and content to the draft guidance immediately above but for a different research area. The relevant information includes such IRB review topics as ***human subject selection criteria***.

The guidance itself is on the Web at https://www.fda.gov/media/142544/download.

For more information, contact the same FDA person listed immediately above.

• **Food and Drug Administration.** Comments are ***due by December 3*** on a new draft guidance titled "Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing." This new draft guidance is designed to:

> "... assist sponsors in the design and analysis of studies that assess the influence of impaired renal function on the pharmacokinetics (PK) and/or pharmacodynamics [PD] of a investigational drug and how such information can impact dosing" (85 Fed. Reg. 55303-55304 at p. 55303, September 4).

The 15-page guidance contains sections of ***special interest for IRBs*** that review such protocols. For example, included in the guidance's six subsections of Section IV ("Study Design") are recommendations that involve ***human subject selection*** such as:

> "• Determination of renal function in ***adults*** ... Design of a ***full*** pharmacokinetic study ... Design of a ***reduced*** pharmacokinetic study ...." (guidance, September, p. 5; on the Web at https://www.fda.gov/media/78573/download).

For more information, contact: Lauren Milligan of FDA's Center for Drug Evaluation and Research at 301-796-5008, or send an email to OCP@fda.hhs.gov.

• **Food and Drug Administration.** Comments are ***due by December 7*** on a new draft 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" (85 Fed. Reg. 63559-63561 at p. 63559).

The guidance contains specific recommendations for researchers ***and the IRBs that review relevant protocols***, such as the following.

> "• Premenopausal women[4] with adequate estrogen suppression[5] and postmenopausal ***women should be equally eligible*** and included in clinical trials for drugs or combinations manipulating the hormonal axis.
>
> [FN #4: See the draft guidance for industry *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms a Recommendations for Clinical Evaluation* (January 2003) ....
>
> FN #5: We acknowledge challenges with defining a cut-off level for estrogen suppression given differences in assays, patient demographics such as weight, medical comorbidities (e.g., polycystic ovarian syndrome), etc.]" (guidance, October, p.2; on the Web at https://www.fda.gov/media/142638/download).

For more information, contact: Jennifer Gao of FDA's Center for Drug Evaluation and Research at 240-402-4683. ©

IRB Compliance Conferences & Courses - By Kathleen J. Maloney, M.Ed., Associate Editor

Readers unable to attend may still access proceedings and any other available conference and course materials

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

- **November 2-12, 2020,** virtual conference: **"MAGI's Clinical Research Conference."** Conference will be presented by MAGI (Model Agreements & Guidelines International). Topics include: regulatory compliance for human subjects research, informed consent, and subject injury. Contact: Norman Goldfarb, Chairman, MAGI, at 650-465-0119.
- **November 12-13, 2020**, live virtual conference: **"Clinical Site Coordinator/Manager and GCP Workshop."** The topics include: elements of informed consent and the reporting requirements for IRBs and Institutional Ethics Committees (IECs). Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org.
- **November 18-19, 2020**, at the Wyndham Lake Buena Vista Disney Springs Resort in Orlando, Florida: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP."** Topics include: informed consent, how FDA performs inspections of clinical investigators, and the duties and responsibilities of Institutional Review Boards (IRBs). Contact: Conference Registrar, SoCRA, at 800-762-7292.
- **December 1-4, 2020**, live virtual conference: **"Clinical Research Monitoring and GCP Workshop for Monitors, Site Coordinators, and Auditors."** Topics include: IRB site visits by agency investigators, and IRB oversight of informed consent. Contact: Conference Registrar, SoCRA, at 800-762-7292, or email to Office@SoCRA.org.
- **December 3-4, 2020,** at the Embassy Suites by Hilton Scottsdale Resort in Scottsdale Arizona: **"Clinical Investigator GCP & Trials Management Program for Clinical Investigators and Key Research Staff."** Topics include: the drug development process, the informed consent process, and safety reporting and serious adverse events. Contact: Conference Registrar, SoCRA at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org. ©

Dennis Maloney, Ph.D., is Editor of the Human Research Report. He earned his degree in Experimental Psychology (with Honors) in 1973. He has authored or edited over 200 works (reference book, textbook chapters, newspaper column, journal articles, etc.), and won over $20 million in grant awards. More of his works are available on the Web at Focus Surveys®.com and at MyLuckyPenny®.com.

Kathleen Maloney, M.Ed., is the Associate Editor of the Human Research Report. She earned her degree in Computers in Education in 1990 and is a former Honors English teacher. She has published nationally, won grant awards, and been honored by a Buffet Foundation. Also an artist, her works (landscapes, seascapes, portraits, etc.) are available in specialty shops and by commission only at KathleenMaloney.net.

Newsletter State Winner
"The Nebraska Gallery of Superb Printing"
Gold Medal - 1994
Gold Medal - 1995
Silver Medal - 1998
Silver Medal - 1999

The HUMAN RESEARCH REPORT is written by **Dennis Maloney, Ph.D.**, and is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold with the understanding that the publisher (**The Deem Corporation**) is not engaged in rendering legal, accounting, or other professional service. If legal advice or other expert assistance is required, then the services of a competent professional should be sought. Preceding statement from a Declaration of Principles jointly adopted by a Committee of the American Bar Association and a Committee of Publishers.

Newsletter National Winner
APEX '96 AWARDS FOR PUBLICATION EXCELLENCE

The subscriber listed below has paid for, and is **licensed to, forward/print/photocopy/distribute the total number of copies of this newsletter that appears in the *red circle below*. Any additional forwarding/printing/photocopying/distributing** of this newsletter is a violation of U.S. Copyright Laws, and **is probable cause for the publisher to file a lawsuit** against the person(s) who forwarded/printed/photocopied/distributed ***more than*** **the number of copies listed in the *red circle below*.**

"X" number of licensed copies

SUBSCRIPTION ACCOUNT NO.
SUBSCRIBER NAME
SUBSCRIBER TITLE
DEPARTMENT/ROOM
ORGANIZATION/INSTITUTION
STREET
CITY STATE ZIP

Contact us at:
Human Research Report • PO Box 451117
Omaha NE 68145-6117 • USA

* * * * *

24/7 Toll-Free *Voice Mail Phone*: 800.786.5748
24/7 Local *Voice Mail Phone*: 402.895.5748
Web Site: https://www.IRBusa.com
Email: Dennis@IRBusa.com

12-Month Subscription Cost for:
• First Subscription = $145/yr.
• Each Extra Subscription = Start Extras Anytime ...ONLY $15/yr.!

BBB MEMBER since 1993
Nebraska, South Dakota, Kansas Plains, and SW Iowa; the BBB OnLine Reliability Program; the **BBB Honor Roll;** and **BBB Rated as A+ ("Excellent")**