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PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRBs and When Protocol Reviews Are Not Required

The federal Office for Human Research Protections (OHRP) in Rockville, Maryland, has issued a new guidance titled "Guidance on Elimination of Institutional Review Board (IRB) Review of Research Applications and Proposals: 2018 Requirements."

This guidance contains recommendations designed to ease IRB burdens. It is one outcome of the many revisions to the traditional "Common Rule" on the protection of human research subjects.

The guidance is intended to lessen or remove any remaining confusion on the part of IRBs and others on what to do, and not do, when reviewing certain research protocols. Such confusion, of course, is the result of many differences between the past "pre-2018 Requirements" in the federal regulations and the subsequent requirements as codified in large part in 2018.

First Formal OHRP Guidance On Elimination of IRB Reviews

OHRP's announcement about the new guidance appears in the FEDERAL REGISTER and it explains, in part, that:

> "The guidance document provides OHRP's first formal guidance on this topic. The document is intended primarily for institutions, IRBs, investigators, HHS funding agencies, and others that may be responsible for the review, conduct, or oversight of nonexempt research involving human subjects conducted or supported by HHS" (85 Fed. Reg. 44311, July 22).

The guidance itself is brief. It focuses mainly on the initial IRB review of a protocol and emphasizes the importance of the date that any applicable research begins. The dates appearing in this guidance are more than mere formalities and specify precisely when elimination of the traditional IRB review is permissible.

> "This guidance represents the Office for Human Research Protections (OHRP's) current thinking on this topic. This guidance does not create or confer any rights for or on any person and does not operate to bind OHRP or the public.
>
> OHRP guidance should be viewed as recommendations unless specific regulatory re-

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

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quirements are cited. The use of the word 'must' in OHRP guidance means that something is required under the Department of Health and Human Services (HHS) regulations at 45 CFR part 46.

The use of the word 'should' in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of 45 CFR part 46.

OHRP is available to discuss alternative approaches by telephone at 240-453-6900 or 866-447-4777, or by email at ohrp@hhs.gov.

Scope: This guidance document applies to nonexempt research involving human subjects that is conducted or supported by HHS. It provides guidance on the elimination of the requirement in section 46.103(f) of the pre-2018 Requirements that each application or proposal for research undergo IRB review and approval as part of the certification process.

This guidance also addresses the requirement in the 2018 Requirements for certification of each proposed research study prior to initiation ...." (guidance, July; on the Web at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/elimination-of-irb-review-of-research-applications-and-proposals/index.html).

Specific Dates Make a Difference

"In this document, the term 'pre-2018 Requirements' refers to subpart A of 45 CFR part 46 (i.e., the Common Rule) as published in the 2016 edition of the CODE OF FEDERAL REGULATIONS. The pre-2018 Requirements were originally promulgated in 1991, and subsequently amended in 2005. The pre-2018 Requirements may also be referred to as the 'pre-2018 Common Rule.'

The term '2018 Requirements' refers to the Common Rule as published in the July 19, 2018 edition of the E-CODE OF FEDERAL REGULATIONS. The 2018 Requirements were originally published on January 19, 2017 and further amended on January 22, 2018 and June 19, 2018. The 2018 Requirements may also be referred to as the 'revised Common Rule.'

Any study initiated[1] on or after January 21, 2019 is required to comply with the pre-2018 Common Rule, unless an institution voluntarily instead elected to transition such studies to comply with the 2018 Requirements.

[FN #1: OHRP interprets 'initiated' to mean research (1) initially approved by an IRB, (2) for which IRB review is waived, or (3) determined to be exempt on or after January 21, 2019 consistent with 45 CFR 101(l).]

That election to transition a study must be documented and dated by the institution or an IRB. (45 CFR 46.101(l). More information about *implementing the revised Common Rule* is available on the OHRP website.

The 2018 Requirements include several provisions pertinent to certification, including the following:

'Certification means the official notification by the institution to the supporting Federal department or agency component, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.' (45 CFR 46.102(a))

Note: The Federalwide Assurance (FWA) is the only type of assurance that OHRP approves" (ibid).

"Certification" of IRB Review Still Required

" 'Certification is required when the research is supported by a federal department or agency and not otherwise waived under 45 CFR 46.101(i) or exempted under 45 CFR 46.104. For such research, institutions shall certify that each proposed research study covered by the assurance and (45 CFR 46.103) has been reviewed and approved by the IRB.

Such certification must be submitted as prescribed by the federal department or agency component supporting the research. Under no condition shall research covered by (45 CFR 46.103) be initiated prior to receipt of the certification that the research has been reviewed and approved by the IRB' (45 CFR 46.103(d)).

Guidance - Pre-2018 Requirements

The pre-2018 Requirements at 45 CFR 46.

103(f) require an institution with an approved assurance to certify to HHS that each application or proposal covered by an OHRP-approved assurance and by 45 CFR 46.103 has been reviewed and approved by the IRB: that is, the research grant application and/or proposal submitted to an HHS component.

Such certifications must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted (45 CFR 46.103(f) of the pre-2018 Requirements ...." (ibid).

2018 "Revised Common Rule" Requirements

"The 2018 Requirements eliminate the requirement in the pre-2018 Requirements that grant applications or proposals for research undergo IRB review and approval for the purpose of certification. Experience suggests that review and approval of the application or proposal is not a productive use of IRB time.

Elimination of that requirement is not expected to reduce protections for human subjects because the research study (e.g. a research protocol) would remain subject to the requirement for IRB review and approval, assuming that an HHS component funds the research.

The 2018 Requirements at 45 CFR 46.103 (d) require certification when the research is supported by HHS, and applicability of the regulations is not otherwise waived under 45 CFR 46.101(i) or the study is not exempted under 45 CFR 46.104.

For such research, institutions must certify that each proposed research study covered by a OHRP-approved assurance and by 45 CFR 46.103 has been reviewed and approved by an IRB. Such certification must be submitted as prescribed by the federal department or agency component supporting the research. Under no condition shall research covered by 45 CFR 46.103 be initiated prior to receipt by HHS of the certification that the research has been reviewed and approved by the IRB.

Thus, for research to which the 2018 Requirements apply, the IRB must review and approve such research (e.g., a research protocol) for certification; however, the IRB no longer is required to review and approve the research grant application or proposal under the 2018 Requirements" (ibid). ©

IRBs, FDA, and Certificates Of Confidentiality (CoCs) - #8

With this article, we conclude our coverage of the FDA's advice to IRBs, researchers, and others on how and when to apply for a special protection for human research subjects; i.e., via Certificates of Confidentiality (CoCs).

Below we present a sample of the exact language that FDA recommends be used when applying to the FDA for a CoC. The full text of that language is contained in the guidance that we have been highlighting; namely, "Certificates of Confidentiality: Guidance for Sponsors, Sponsor-Investigators, Researchers, Industry, and Food and Drug Administration Staff."

"We recommend use of the following language in the request letter to facilitate FDA's review:

The requestor is engaged in biomedical, clinical, or other research, in which identifiable, sensitive information is collected or used" (https://www.fda.gov/media/132966/download).

Researchers Must Agree to Not Disclose Human Subject Information, Even in Court

"*The requestor agrees that it is responsible for complying with requirements to protect the confidentiality of identifiable, sensitive information that is collected or used in biomedical, behavioral, clinical, or other research.*

The requestor agrees not to disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains ....

After FDA completes its review [of the application], the Center will send an electronic response letter to the requestor indicating whether or not the discretionary CoC has been granted. If granted, that electronic response letter will serve as the CoC ...." (guidance, pp. 6-7). ©

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IRBs and Use of HIPAA Review Exemption - #14

With this article, we conclude our coverage of an important set of recommendations from the Secretary's Advisory Committee on Human Research Protections (SACHRP) for IRBs and researchers that is titled "Attachment B - Recommendations on the Interpretation and Application of §__104(d)(4) the 'HIPAA Exemption.'"

As is typical of many SACHRP documents, this set of recommendations was an attachment to a cover letter that was submitted to HHS. The recommendations are currently under review by HHS.

Due to more recent and pressing IRB issues, we have been interspersing our articles on this IRB review exemption with other topics ... until now.

The "HIPAA Exemption" allows IRBs to waive their reviews, and the need for informed consent, for certain secondary research projects involving identifiable private information or identifiable biospecimens (e.g., see HRRs for May, 2019 through September, 2019, and for December, 2019 through April, 2020). We resume below with SACHRP's final note about this IRB exemption, related state laws, and FDA requirements.

State Laws Sometimes Overlooked By IRBs

"With respect to state law requirements, many states treat certain categories of personal health information as particularly sensitive and afford such information additional protections.

California, for example, requires that health records relating HIV/AIDS may not be disclosed except pursuant to limited public health exceptions or written authorization by the person who is the subject of the record or his/her guardian.

Several states, including New York, ban genetic testing results from being disclosed except as authorized in writing by the test subject (i.e., in the informed consent form).

Research institutions - particularly institutions conducting research in many different states - are often less familiar with these supplemental state requirements than with federal HIPAA and Common Rule requirements, and it is therefore extremely important that they review carefully whether particular state-level consent requirements may apply, even if the research otherwise qualifies for the HIPAA Exemption.

Unless and until the FDA or state agencies issue regulations or guidance that would seek to harmonize a particular supplemental legal requirement with the HIPAA Exemption, the HIPAA Exemption serves only to exempt research from Common Rule requirements and does not speak to how such research activities should be treated under these applicable frameworks.

The Common Rule reinforces the fact that it does not serve as a substitute for other federal or state laws or regulations that provide additional protection for human subjects, stating that 'compliance with this policy requires compliance with pertinent federal laws or regulations that provide additional protections for human subjects' and 'this policy does not affect any state or local laws or regulations ... that may otherwise be applicable and that provide additional protections for human subjects'" (SACHRP Recommendations, December 12, 2017; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-december-12-2017/index.html).

Complex Requirements to Forego IRB Review

"Thus, investigators must obtain informed consent or waiver of consent for any studies that are subject to FDA jurisdiction unless and until the FDA issues new guidance to the contrary and must always review whether additional state-level clinical or research-related protections may apply" (ibid).

The reason behind our presentation in the HRR of the IRB-related details contained in these SACHRP Recommendations on the HIPAA Exemption is emphasized by the SACHRP itself, as follows.

"The application of this new exemption - like the application of HIPAA itself - is complex, and without sufficient guidance, research institutions, IRBs, and the general public may have difficulty understanding the circumstances under which the HIPAA Exemption may and may not be relied upon as an exemption from Common Rule requirements.

Understanding the contours of the HIPAA Exemption will be significant for researchers involved in secondary research activities, particularly records research, as investigators conducting research activities that qualify for the exemption will be permitted to forego the requirement of securing IRB approval and informed consent (traditional informed consent, or 'broad consent') or waiver of consent for such secondary research" (ibid). ©

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IRBs and "Key Information" In Informed Consent - #5

We continue in this article with our coverage of a very useful set of IRB recommendations released by the Secretary's Advisory Committee on Human Research Protections (SACHRP). As usual, the recommendations appear in an attachment to a letter submitted to the Secretary of the Department of Health and Human Services (HHS).

The recommendations address a number of major informed consent issues. They comprise the SACHRP's response to a series of six consent questions posed to it by the federal Office for Human Research Protections (OHRP).

In turn, the OHRP questions are based on questions frequently posed to OHRP by IRBs throughout the country.

We resume with more of the SACHRP's response to "Question 5" from OHRP that addressed several benefit and risk topics in human subjects research, as follows below.

See HRRs for September 2019, October 2019, February 2020, and March 2020 for previous installments in this series of informed consent articles.

Consent Must Show That Research Is Not the Same As Treatment

"Implicit in consideration of how best to present risks of harm and potential benefits to potential subjects is the concern that patients who are potential subjects may not fully appreciate that research - even research that has some potential to benefit them directly - has the primary goal of advancing knowledge rather than delivering treatment.

Discussing potential benefit may pose a particular challenge. Potential direct benefit to subjects should not be overstated and should be distinguished from the anticipated value or societal benefit of the research in simple and straightforward terms.

SACHRP is aware that some IRBs have responded to concerns about potential subjects' overestimation of direct benefit by minimizing information about potential direct benefit in the consent form, reasoning that subjects will thus be less likely to believe that therapy and research are governed by the same primary goal of advancing the individual patient's best interest.

However, because patients who are potential research subjects often approach clinical trials with the hope of direct benefit, minimal or vague language about potential direct benefit does not correct that misperception.

Potential benefits are a legitimate consideration in a individual's decision to enroll; it is acceptable to include an accurate and specific description of potential benefit as key information" ('Attachment C - New 'Key Information' Informed Consent Requirements,' October 17, 2018, pp. 7-8 of 12; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-november-13-2018/index.html).

Uncertainty Is Normal When Weighing Risks and Benefits

"Finally, Question 5 asks, 'Specifically, how do different study designs affect: (1) which reasonably foreseeable risks and potential benefits should be included in the discussion of key information, and (2) how such risks and benefits should be described in the discussion of key information?'

As discussed above in our response to Questions 1, 3 and 4 [see previous HRRs], different study designs and facts of the study do affect which risks and benefits should be included and described as key information.

However, as noted in that response, SACHRP did not find any single tool that was sufficient to identify the key information for every type of clinical trial, and that conclusion also applies to the identification of risks and benefits as key information as targeted here in Question 5.

Because there is great variability across clinical trials, there may be great variability in the choice and presentation of key information.

SACHRP further notes that existing elements of consent, and traditional approaches to consent, have emphasized benefit and risk, but have not given similar attention to burdens or to the impact of participation in research on an individual's normal life activities.

The flexibility provided by the key information summary should be used to address such impact in addition to providing a more focused overview of risk and benefit.

In many cases, impact is certain, but benefits and harms are not." © {TBC}

IRBs and Developing Drugs and Biologics During COVID-19 -- #3

We continue here with FDA's recent guidance titled "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention" (see https://www.fda.gov/media/137926/download). This guidance is packed with practical tips for IRBs and researchers.

We resume where we left off last month, in which FDA advises on what to do in the early stages of an experiment, as follows:

> "In instances where there is some but limited information supporting the potential for efficacy, approaches where an initial assessment of potential benefit can be made before enrolling a large number of subjects are appropriate. These approaches may include the following:
>
> -- Conducting an initial small, controlled trial to assess for drug activity (proof-of-concept) that suggests the potential for clinical benefit" (guidance, p. 7).

Data Monitoring Committee Recommended

> "-- Conducting a trial that incorporates prospectively planned criteria to stop the trial for futility (i.e., with the prospect of expanding from a proof-of-concept phase to a larger confirmatory trial). Such a trial might also incorporate additional prospectively planned adaptations (see additional comments on adaptive design proposals below).
>
> • FDA encourages sponsors to use an independent data monitoring committee (DMC) to ensure subject safety and trial integrity.
>
> -- Sponsors should submit the DMC charter as early as possible.
>
> -- Sponsors should ensure there will be appropriate DMC monitoring to safeguard the welfare of subjects, accounting for important factors such as the expected enrollment rate, the expected lag time to analyze interim data for DMC meetings, and the frequency of DMC meetings.[21]
>
> [FN #21: FDA has proposed relevant recommendations in the draft guidances for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006) and *Safety Assessment for IND Safety Reporting* (December 2015). When final, these guidances will represent the FDA's current thinking on these topics.]
>
> -- If enrollment is anticipated to be rapid, but additional safety data are needed before dosing a large number of subjects, an enrollment pause could be built into the trial. In this case, enrollment would be temporarily halted, and the DMC would assess the data and then recommend that the trial or dosing group either terminate or resume enrollment.
>
> • FDA encourages sponsors to incorporate prospectively planned criteria to stop the trial for futility (lack of efficacy) or harm in any confirmatory trial. The stopping criteria should aim to ensure a high probability of halting the trial if the drug is harmful (e.g., associated with a higher risk of death), a reasonable probability of halting the trial if the drug is ineffective, and a high probability of continuing the trial if the drug is effective" (supra at pp. 7-8).

Another Reason for Subject Enrollment Pause

> "If accrual in such a trial is expected to be rapid, an enrollment pause may be considered to support stopping for futility.
>
> • If a trial incorporates the possibility of early stopping for evidence of benefit or any adaptations to the sample size, dosing arms, or other design features, sponsors should prospectively plan the design in a manner to ensure control of the type I error rate and reliable treatment effect estimation ....
>
> An independent committee, such as a DMC, should be tasked with providing any recommendations for early termination or design adaptations based on unblinded interim data.
>
> • FDA anticipates events that occur outside of an ongoing trial may provide important new information relevant to the ongoing trial (e.g., changes to the standard of care) and may motivate revisions to the trial design. Well-motivated changes based on information external to the trial can be acceptable and sponsors are encouraged to discuss these changes with the FDA.
>
> **C. Efficacy Endpoints**
>
> Sponsors of drugs to treat or prevent COVID-19 should consider the following:
>
> • The drug development program should evaluate the effect of the investigational drug relative to placebo on clinically meaningful aspects of the disease. The relevance and appropriateness of measures may depend on the population studied, the clinical setting, and/or baseline disease severity ...." (supra at p. 8). © {TBC}

IRBs and COVID: Statistical Considerations in Studies - #2

We continue here with a topic we introduced in the July HRR; namely, special statistical considerations for IRBs and researchers who are involved with clinical trials during the current pandemic (see our recent July "Compliance Comment Deadlines & Notices" section).

As we noted then, the COVID pandemic is affecting many types of studies, including ones that are not directly involved with the virus itself. Hence, FDA is warning the research compliance community of special factors to heed for the protection of human research subjects.

FDA's new guidance in this area is titled "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency." We have already presented the guidance's view on major complications posed for research subject recruitment and retention due to the pandemic.

While we do not often cover statistical issues in human research, they can affect the design and results interpretation of said studies. We resume below with more of FDA's recommendations in this area as contained in the guidance's section titled "A. Trial Integrity."

Possible Bias and Role of Blinded Trials

"• When considering modifications to the trial to address the impact of COVID-19, sponsors should not propose any trial modifications based on data that may introduce bias into the interpretation of trial findings.

Generally, for a blinded trial, modifications based on information that reveals the magnitude of the treatment effect or information presented by treatment arm have the potential to introduce bias.

For example, stopping a trial before its planned duration based on knowledge of a treatment difference between arms from a previous interim analysis may introduce bias by stopping a trial close to a random high treatment estimate. Histograms and Kaplan–Meier plots may suggest treatment effect information and should be avoided.

However, with appropriate safeguards for the integrity of the trial, such as the use of a Data Monitoring Committee, a trial may be stopped for the safety of the participants based on unblinded data.

• Appropriate participant data to consider when making modifications to the trial to address the impact of COVID-19 include summaries pooled over treatment arms including information on missing data, participant treatment discontinuation or interruptions, participant trial withdrawal, and endpoints.

Information not specific to individual participants, such as information on site closures and disruption of the supply of investigational product, may also be appropriate to use when considering modifications to the trial.

B. Trial Mitigation and Analysis Strategies

To address the impact of COVID-19 on evaluating the primary and key secondary endpoints of the trial, FDA provides considerations below for several design and analysis strategies. Multiple strategies may be needed to address the impact of COVID-19 adequately. These design and analysis strategies should be discussed with the relevant FDA review division" (guidance, June, p. 3; on the Web at https://www.fda.gov/media/139145/download).

If a Trial Is Stopped

"(1) ... it is important to capture specific information at the participant level, describing the context and/or reasons for post-baseline events as they relate to COVID-19, such as discontinuation of treatment, withdrawal from the trial, use of alternative or rescue treatments, missed endpoint ascertainment, and the use of alternative endpoint ascertainment methods.

This information may be useful for incorporating into analysis strategies to address potential biases or for performing sensitivity analyses related to the impact of COVID-19.

(2) For sponsors considering stopping a trial and conducting a final analysis, a major consideration is the loss of statistical power from a smaller sample size or less follow-up time than was anticipated. For a blinded trial, a blinded power assessment could be conducted to estimate the power of the modified study.

The assessment could use the actual event rates pooled over treatment arms or the observed variability pooled over treatment arms in the completed portion of the trial." © {TBC}

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IRBs and Eligibility of Subjects In Clinical Cancer Trials -- #1

FDA recently issued four separate guidances on clinical cancer trials eligibility criteria for human research subjects. Each guidance covers a different group of eligibility criteria or areas, with advice for IRBs and researchers on how to address the application of said criteria.

The first guidance (in chronological publication order) is titled "Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients."

The three subsequent titles, each beginning first with "Cancer Clinical Trial Eligibility:" are "... Patients With Human Immunodeficiency Virus, Hepatitis B Virus, or Hepatitis C Virus Infections," "... Brain Metastases," and "... Patients With Organ Dysfunction or Prior or Concurrent Malignancies."

Past Subject Eligibility Criteria Too Restrictive

In addition to the obvious differences in eligibility issues inherent in the different guidances, there are some general areas that apply to all of them.

These includes topics for careful IRB consideration, since the factors involved have clear implications for subject safety and assessment of risk-benefit ratios and are worth reiterating. For example:

> "A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed, taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of the adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial.
>
> However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.
>
> Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice and should be considered to avoid jeopardizing patient safety.
>
> Early evaluation and development of potentially effective drugs, particularly targeted drugs, in pediatric patients may provide information on safe and effective use, therefore reducing risks associated with off label use, and accelerate the development of effective, innovative therapies for pediatric patients" (85 Fed. Reg. 41989-41990 at p. 41990, July 13).

Since these subject eligibility factors are similar for other populations, after allowing for unique differences between varying underlying human subject conditions, we will not repeat them when discussing the four different guidances.

Unnecessary Delays in Developing New Drugs for Many Children

In the present article we focus on crucial eligibility factors for pediatric populations in clinical cancer trials. For example, this pediatric-oriented guidance:

> "... includes recommendations regarding minimum age eligibility criteria and addresses specific situations in which the inclusion of children (for the purposes of this guidance, ages 2 to younger than 12 years) and adolescents (for the purposes of this guidance, ages 12 years to 17 years) is appropriate in cancer trials (i.e., based on disease biology and clinical course, molecular target of the investigational drug, and/or its molecular mechanism).
>
> In addition, the guidance includes ethical and regulatory considerations for including pediatric patients in such trials" (ibid).

This seven-page guidance describes why its IRB and researcher recommendations are so badly needed, as follows:

> "Historically, pediatric patients have not been included in adult clinical trials, which generally specify 18 years as the minimum age of eligibility. Pediatric trials of the same drug generally have been initiated after the completion of one or more adult clinical trials, or after the initial approval in adults, delaying development of and access to potentially effective new cancer drugs for the pediatric population" (guidance, p. 2; on the Web at https://www.fda.gov/media/121318/download)."

© {TBC}

Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** Comments are being accepted ***until September 21*** on a new draft guidance titled "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research."

> "Cannabis and cannabis-derived compounds have been the subject of interest from consumers, industry, researchers, the public, and regulators.....
>
> This draft guidance outlines FDA's current thinking on several topics relevant to the development of drugs containing cannabis and cannabis-derived compounds: (1) The source of cannabis and cannabis-derived compounds ***for clinical research***; (2) general quality considerations for developing drugs that contain cannabis and cannabis-derived compounds; and (3) calculation of percent delta-9 THC in botanical raw materials, extracts, and finished products" (85 Fed. Reg. 44305-44306, July 22).

The seven-page guidance contains recommendations for researchers (and, by default, for ***potential IRB reviewers***) in three areas: the sources of the cannabis, resources for information on quality considerations, and percent of Delta-9 THC calculation. The guidance itself is on the Web at https://www.fda.gov/media/140319/download).

For more information, contact: Ann Muhlberg of FDA's Center for Drug Evaluation and Research at 240-402-6901.

• **Food and Drug Administration.** Comments are being accepted ***until September 28*** on a new draft guidance titled "Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biological Products."

> "When finalized, this guidance will describe FDA's current recommendations about endotoxin limits in investigational oncology drugs and biological products. ***It looks at a risk-based approach of weighing the potential risks*** of not evaluating endotoxin levels in all components of multidrug regimen against the potential benefits to patients with serious and life-threatening diseases.
>
> It is limited to anticancer drugs administered parenterally (except for intraocular administration) to treat serious and life-threatening cancers based on histology or stage of disease" (85 Fed. Reg. 45643-45644 at p. 45644, July 29).

This guidance addresses several ***risk-benefit issues*** of practical import for affected research subjects, for the researchers working with those patients, and ***for the IRBs that review and monitor applicable protocols***. For example:

> "Investigational drugs for treating patients with incurable cancers who have short life expectancy are often studied in continuation with approved drugs in an attempt to identify multidrug or multimodality regimens that may prolong survival.
>
> Administration of one or more drugs within the same 60-minute time frame as the investigational drug may pose challenges regarding the endotoxin limits for that investigational drug at a time when the manufacturing process for that investigational drug has not been optimized.
>
> This guidance addresses endotoxin limits for investigational drugs for the treatment of advanced cancer, when evaluated in early (pilot) clinical trials as part of a multidrug regimen" (guidance, p. 2 of 6; on the Web at https://www.fda.gov/media/140410/download).

For more information, contact: Patricia Keegan of FDA's CDER at 301-796-1387.

• **Office for Human Research Protections.** The OHRP is scheduled to review any comments it received regarding its recent request to the Office of Management and Budget (OMB) for a three-year extension of the record keeping and reporting requirements associated with the ***"Federalwide Assurance Form" (FWA)***.

> "The FWA is designed to provide a simplified procedure for institutions engaged in HHS-conducted or supported research to satisfy the assurance requirements of Section 491(a) of the Public Health Service Act and ***HHS Regulations for the protection of human subjects*** at 45 CFR 46.103.
>
> Respondents are institutions engaged in human subject's research that is conducted or supported by HHS" (see 85 Fed. Reg. 43858-43859 at p. 43859, July 20).

The Department of Health and Human Services (HHS) estimates that there are approximately ***14,000 institutions or organizations affected by the FWA requirements***.

For more information, contact: Sherrette Funn at 202-795-7714, or via email to Sherrette.Funn@hhs.gov, citing FEDERAL REGISTER Document Identifier OS-0990-0278. ©

FDA Warning

(Unless noted otherwise, recipients of a Warning Letter have 15 days to fix problems or explain how and when they will fix them. If not, they face sanctions with no additional warning and possible permanent disqualification from ever conducting research again with FDA-regulated products. This HRR feature includes Warning Letters sent to researchers, administrators, sponsors, and Institutional Review Boards.)

Warning Letter To: Texas Physician (Part 2)
Warning Letter Date: June 28, 2016
Investigation Period: February 1-18, 2016
Noncompliance: Failing to Follow Approved Research Plan

* * *

Researcher Exposes Human Subjects To Unnecessary Experimental Risks

We continue this month with more of the details describing how the researcher failed to follow his own approved research plan. These details are important because they exemplify the kinds of behaviors (or the lack thereof) that "trip up" a researcher and can lead to federal investigations and sanctions.

Even more importantly, these research methodology details highlight unacceptable risks for human subjects due to lapses in researcher attention and activity. For example, last month we presented one FDA finding in this case wherein a human subject should have never even been enrolled!

Further, as we shall see, at least two subjects were unnecessarily exposed to risks, again due to the failure of the researcher to follow his study plan.

> "b. Subjects 110946 and 112166 were initially overdosed with study drug because you did not have required serum creatinine and eGFR values at the time the subjects were randomized and received study drug ....
>
> The failure to have serum creatinine and eGFR values at the time of randomization compromises subject safety as one subject was later found to be ineligible for the study and two other subjects received incorrect initial doses of study drug and required down titration.
>
> In your March 4, 2016 written response to the Form FDA 483, you indicate that during the early part of the study, subjects were enrolled from your own clinic database and medical records were readily available so you followed the protocol.
>
> You state that in the later part of study, subjects were referred to your site using ... [redacted by FDA] to help facilitate subject recruitment. At that point, you state you could not confirm the required serum creatinine value or obtain medical records at Visit 1, so you erroneously relied on subject verbal history.
>
> Further, you explain that you contacted subjects and made efforts to obtain documented laboratory values. Once these values were obtained, you indicate that subjects were placed on the correct dose of study drug if adjustment was necessary. You describe how subject safety was ensured as all enrolled subjects had regular visits with their nephrologist or primary care physician (PCP)."

Since Medical Records Can Just Slow You Down, Let's Just Ask the Subjects What They Recall

> "With regard to Subjects 110946 and 112166 being overdosed with study drug and requiring down titration, you indicate that you relied on subject-reported kidney history and made the following assumptions about their diabetes medications:
>
> Subject 110946 was taking metformin 2000 mg as prescribed by her PCP. You explain that because that dose of metformin is only permissible in subjects with no renal impairment (i.e., eGFR >60 mL/min/1.73m2), the subject was assigned 100 mg of study drug, but was later down titrated to 50 mg when you received her medical records.
>
> Subject 112166 was taking metformin 1000 mg with glyburide 5 mg. You explain that these medications and doses are indicative of no renal impairment, so the subject was assigned 100 mg of study drug, but was later down titrated to 50 mg when you received the medical records.
>
> You acknowledge that the initial study drug dose should not have been determined without first obtaining the required laboratory results, and that a more thorough screening process should have been done prior to assigning study drug dose.
>
> You state that staff has been retrained on assigning correct study drug dose and to not randomize or dispense study drug based on subjects' verbal history. Such that [sic], your site will require subjects to have medical records in-hand at Visit 1, including current serum creatinine values, before randomization and assignment of study drug dose." © {TBC}

In Court

This HRR feature includes lawsuits filed by former research subjects, researchers, and others over ***key research compliance issues***. Institutional Review Boards (IRBs), Institutional Biosafety Committees (IBCs), Conflict of Interest (COI) Committees, Data Safety Monitoring Boards (DSMBs) and Research Misconduct Committees may be involved. Members of such compliance committees often serve on more than one such committee.

* * *

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 41)
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

Key Role of Human Subjects "Assurance Agreement"

As we described last month, the former research subject in this case claimed that she was a "third party beneficiary" to the traditional Assurance Agreement that the university had obtained from OHRP.

The OHSU disputed that but it did discuss the applicability of the "Belmont Report" that the research subject said applied and that also bound OHSU to protect human research subjects. The university said:

> "The Belmont Report (which, plaintiff alleges, is incorporated by reference into the Assurance Agreement) was drafted in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ....
>
> The Belmont Report was 'a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects,' and did not 'make specific recommendations for administrative action by the Secretary of Health, Education and Welfare' ....
>
> 45 C.F.R. §46.101, *et seq*. sets forth the DHHS' policy regarding human research subjects protection. Every institution engaged in human subjects research supported by the DHHS must obtain an 'assurance of compliance' with the regulations. 45 C.F.R. §46.103 (a). Continuing compliance with the regulations is a condition precedent of federal funding for research involving human subjects. 45 C.F.R. §46.122.
>
> In 1996 OHSU obtained an assurance of compliance in accordance with 45 C.F.R. §46.103 (a), embodied in a document entitled 'Multiple Project Assurance Agreement for the Protection of Human Subjects' (the 'MPA').
>
> The MPA was renewed in March 2001 under a document entitled 'Department of Health and Human Services Federalwide Assurance of Protection for Human Subjects' (the 'FWA') ...." ("Memorandum in Support of Defendants Oregon Health and Science University, Linn Goldberg, Diane Elliot, Kerry Kuehl, Esther Moe, and David MacKinnon's Motion to Dismiss; or, in the Alternative, to Strike Certain Allegations," November 4, 2002, Docket Document #20, pp. 38-39).

Federalwide Assurance (FWA) Was Approved and In Place

> "The MPA provides, among other things, that OHSU 'is guided by the ethical principles regarding ALL research involving humans as subjects, as set forth in the Belmont Report, regardless of whether the research is subject to Federal regulation or with whom conducted or source of support (i.e., sponsorship)' ....
>
> Like the MPA, OHSU's FWA assures the DHHS that 'all of its activities related to human subject research, regardless of funding source, will be guided by the ethical principals [sic] in The Belmont Report' .... Without the MPA or FWA (collectively, the 'Assurance) in place, OHSU would not have been able to obtain or maintain DHHS funding for the Study.
>
> Assuming that plaintiff is correct that the Assurance Agreement is a government contract, and that plaintiff somehow benefitted indirectly from the obligations undertaken therein, it is well settled in the Ninth Circuit that 'parties that benefit from a government contract are generally assumed to be incidental beneficiaries, and may not enforce the contract absent a clear intent to the contrary.' *Klamath Water Users Protective Assoc. v Patterson*, 204 F.3d 1206,1212 (9th Cir. 2000) (underline emphasis added)" (supra at pp. 39-40). © **{TBC}**

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.

. • **September 14-16, 2020**, at The Carolina Inn in Chapel Hill, North Carolina: **"The Three I's (IACUCs, IBCs, & IRBs) - Research Integrity & Biosecurity Conference."** Topics include: ethical concerns of foreign influence, research risk assessments, and integrity in the era of social data. Contact: Lynne Walsh, Massachusetts Society for Medical Research, at 978-251-1556, or email to msmr@att.net.

• **September 17, 2020**, iWebinar (8:10 am - 4:00 pm): **"Practical & Ethical Considerations for Single IRB Review."** This is a federal Office for Human Research Protections (OHRP) "Exploratory Workshop." The topics will include: providing options and ensuring quality in single IRB reviews, effectively managing local context, and sharing responsibilities and distinguishing roles in human studies. Contact: Yi-Chiu (Debbie) Fan at 240-453-8142, or send email to Yi-Chiu.fan@HHS.gov.

• **September 22-23, 2020**, at the Forum Events Center in Fishers, Indiana (suburban Indianapolis): **"Beyond Good Enough: Enhancing the Integrity of Human Subjects Research."** This is a federal Office for Human Research Protections (OHRP) Research Community Forum. Topics include: secondary research with data and specimens, informed consent, and research misconduct v. IRB noncompliance. Contact: Ms. Beth Johnson at 317-278-7831, or send an email to bwinnie @iu.edu.

• **September 23-26, 2020, as a virtual conference. "2020 SoCRA Conference."** Topics include: human subject enrollment, retention, and informed consent; and numerous IRB and research ethics issues. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **October 17-21, 2020**, at the Sheraton Boston Hotel in Boston, Massachusetts: **"SRA International Annual Meeting Boston 2020."** Topics include: a Responsible Conduct of Research (RCR) Expo held in conjunction with the federal Office of Research Integrity (ORI) presentation, ethical challenges in human subjects research, and IRB review of social and behavioral research protocols. Contact: SRA International, at 703-741-0140, or send an email to info@srainternational.org.

• **October 22-23, 2020**, at the Wyndham Philadelphia Historic District in Philadelphia, Pennsylvania: **"Clinical Research Monitoring and GCP Workshop."** Topics include: obligations of sponsors and monitors as required by the Food and Drug Administration (FDA), site visits and how to meet with investigators, and IRB oversight of informed consent. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org.

• **October 26-30, 2020**, at the Embassy Suites by Hilton Scottsdale Resort in Scottsdale, Arizona: **"Clinical Research/ Clinical Science Course."** Topics include: IRB review guidelines, informed consent, and key ethical issues in clinical trials. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org. ©

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