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Human Research Report

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRB Reviews, Use of Placebos, And Double-Blinding - #1

The use of placebos and blinding (including double-blinding) are traditional research design features used to remove both possible human subject bias (or expectations) and researcher bias.

However, for IRBs reviewing certain types of high-risk experiments, the use of such techniques may not be approvable. Accordingly, FDA has released a revised guidance that should prove useful for applicable IRBs.

> "The ... FDA ... is announcing the availability of a final guidance for industry entitled 'Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products.'
>
> This guidance provides recommendations to industry about using placebos and blinding in randomized controlled clinical trials in development programs for drug or biological products to treat hematologic malignancies and oncologic diseases regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER)" (84 Fed. Reg. 45496-45497 at page 45496, August 29).

Using Placebos and Possible Ethical Concerns

> "Placebos, defined as inert substances with no pharmacologic activity, are commonly used in double-blind, randomized controlled clinical trials.
>
> Blinding investigators and patients in these trials to the treatment [that] patients are receiving decreases the likelihood of biased observations of the effectiveness outcomes, may decrease differential patient drop out, and allows for unbiased observation of outcome measures, which are particularly important when the assessment includes subjective endpoints.
>
> For example, a placebo-controlled study design may be useful or preferred in maintenance therapy, in add-on trial designs, in trials of adjuvant therapies (for which standard of care is surveillance), and for indications where no treatment is available (best supportive care can be added to both arms to ensure all available care is provided to patients).
>
> However, in development programs for malignant hematologic and oncologic disease, the use of a placebo in double-blind, randomized controlled clinical trials may present practical and ethical concerns.
>
> In many cases, because of the toxicity profile

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 of our choice in brackets [ ] to make the material easier to read, or edit paragraph formatting.

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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of the active treatment, patients and investigators may infer which treatment patients are receiving, so using a placebo control may not blind the treatment. For patients with hematologic malignancies and oncologic diseases that have standard effective therapy available, using a placebo (not an active treatment) generally would not be considered ethical, so an active control trial should be conducted.

One such active control superiority trial design option is to conduct an open-label trial with a physician's choice of one of a few standard therapies as the comparator. In open-label comparative trials for which investigator bias may be of concern, a blinded central independent review of scans may mitigate bias regarding endpoint assessment.[3]

[FN #3: See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.]" (guidance, August, pp. 1-2; at https://www.fda.gov/media/130326/download).

Continued Blinding Can Cause Problems

"Another option has been to compare the investigational drug product with the placebo, with each added to the standard of care (an add-on trial).

Continued blinding of patients and investigators at the time of disease progression or occurrence of serious adverse events is usually not acceptable. In a blinded immunotherapy trial, for example, a patient who develops suspected drug-related serious adverse events on the control arm may receive unnecessary treatments (e.g., immunosuppressive drug products including a high dose of glucocorticoids, cyclophosphamide, interleukin-6 antagonist, or infliximab) for management of adverse events incorrectly attributed to the investigational drug product.

Maintaining the blind after disease progression could also affect the selection and timing of a patient's subsequent therapy, potentially preventing a patient who had been on a placebo arm from receiving an approved therapy or delaying or preventing the patient's entry into other clinical trials (for those trials of similar drug products that may have specific exclusion criteria based on prior treatment with an active drug or class of drugs). Unblinding in those cases would therefore allow informed decision-making about additional treatment options (see below).

III. CONSIDERATIONS FOR USING PLACEBOS AND BLINDING

Given that using a placebo in randomized controlled clinical trials of therapies to treat hematologic malignancy and oncologic disease for which there is known effective therapy is ethically unacceptable, sponsors should consider using a placebo-controlled design only in selected circumstances (e.g., when surveillance is standard of care) or with certain trial design features (e.g., when the trial uses an add-on design)" (pp. 2-3).

Specific Consent Element for IRB Reviews

"When considering a placebo control, sponsors should take the following into account:

• Sponsors should provide the rationale for the trial design. Justification is particularly important in the setting of a sham surgical procedure, when invasive methods are required to administer a placebo (e.g., intrathecal administration, intratumoral administration, repeated intravenous administration via an indwelling catheter), when primary adverse event prophylaxis is required (e.g., antihistamine, acetaminophen, and/or corticosteroids to prevent infusion reaction), when there is an available therapy, or when a placebo is given as monotherapy and not combined with an active drug or drugs.

• FDA does not require patient-level maintenance of blinding at the time of disease recurrence or progression. Unless there are no available appropriate treatment alternatives, FDA recommends unblinding only the patient and the investigator at the time of documented disease recurrence or progression by an objective measurement or measurements to ensure optimal patient management. If sponsors intend to maintain patient-level blinding when disease recurs or progresses and there are existing available treatments, the informed consent document should acknowledge the risks of this approach, and the protocol should include justification for the potential added risk" (ibid). © {TBC}

IRBs and "Key Information" In Informed Consent - #2

With this article, we continue our coverage of an area vital to any IRB review; namely, the adequacy of the informed consent for the human subjects participating in an experiment. Our focus here is on new consent requirements being activated by the revised Common Rule on protecting human subjects.

The specific recommendations that we present originated with the federally-sponsored Secretary's Advisory Committee on Human Research Protections (SACHRP).

As we introduced with our initial article on this topic last month (see pp. 1-2, September HRR), the SACHRP has responded to a series of six questions posed to it by the federal Office for Human Research Protections (OHRP).

As SACHRP explains, the committee decided to lump some of OHRP's questions together (regardless of their numerical order) because of their common themes, and then address the different questions accordingly. Below we begin presenting said questions/answers.

Are "Key Information" Items All the Same?

"Question 1:

How does 'key information' [in informed consent documents] *vary depending on the clinical trial design being used, the specific research questions being asked, and the populations being asked to participate?*

For instance, examples of various trial designs that might impact considerations for key information include:

(1) a trial where subjects have a terminal disease where current treatment does not fully cure it, and the trial involves randomization between current standard care and a new unapproved treatment that might involve much greater side effects than standard care, but a better chance of a cure;

(2) the same type of circumstance, but where the new treatment is already on the market, but being used for a different purpose; and

(3) a randomized trial comparing standard care (which is very effective) to an unapproved new drug ....

What are the primary considerations and influences that should be described for the various types of clinical trial designs?

Question 3:

Are there criteria, thresholds, or standards that can be identified to determine what information should be included as 'key' and what are the underlying justifications or principles supporting them?

Question 4:

*Given the wide variety of types and complexities of studies, and drug/device/biologics considerations, what tool(s) or strategies do you recommend to assist investigators and IRBs in determining the key information to be presented up front (e.g., developing a table or algorithm, general points-to-consider)?***"** ("Attachment C - New 'Key Information' Informed Consent Requirements," October 17, 2018, pp. 3-4 of 12; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-november-13-2018/index.html).

"Key Information" Can Vary Widely Among Different Studies

"Response to Questions 1, 3 and 4:

Taken together, questions 1, 3[,] and 4 in essence ask whether there are any considerations, criteria, thresholds, standards, tables, algorithms, or general points-to-consider that could be used to identify key information for a given clinical trial. We will refer to these collectively as 'tools.'

SACHRP looked at a variety of possible tools to serve this purpose. We concluded that the development of such a tool is not a simple matter. Even when narrowing the focus from all human subjects research to the subset of clinical trials, there is substantial complexity and variability in trial design, types of interventions, disease states, and potential subject populations.

Examples of some of those tools are presented in Appendices I through III [to be presented in a future HRR]. Although the committee did not identify a single tool that it felt confident could identify key information for all studies and all participants, that does not mean it is an impossible task.

Tools and guidelines can help with consistency in both the writing and review of consent forms, but their development will be an ongoing process. SACHRP recognizes that significant creativity exists within the regulated community and encourages continued efforts to develop and test potential tools.

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

The existing system of drafting consent forms and obtaining consent has become stagnant, and it needs to improve**"** (ibid). **© {TBC}**

IRBs and Which Regulations Apply For How Long? - #6

We continue here with presenting highlights of a federal guidance for IRBs and others regarding how to "transition" to the requirements of the revised Common Rule. In previous articles in this series we have described important new changes to informed consent and other IRB matters, and how different compliance dates affect current and past IRB reviews (e.g., see last month's September HRR installment on p. 6).

The relevant guidance from the federal Office for Human Research Protections (OHRP) is titled "The Revised Common Rule Compliance Dates and Transition Provision (45 CFR 46.101(l)) January 2019."

We continue here where we left off last month. At that point, we introduced the topic of IRBs' "continuing reviews" whereby OHRP advised that there are circumstances in which an institution may need or wish to conduct continuing IRB reviews even when the regulations do not require it. In such instances, OHRP states, there are two "Pathways" that an IRB can follow. We presented Pathway #1 last month.

We concluded last month's article by noting that certain new regulatory requirements would still apply, even under "Pathway 2," as they appear below.

Is Continuing IRB Review Warranted?

"These requirements can be satisfied as long as an IRB determines that continuing review is warranted, either on a study-specific basis or with respect to broader categories of research, and the rationale for this determination is documented.

Given that the regulatory language refers to an IRB's determination, an institutional policy would not satisfy this requirement without the involvement of an IRB. However, an IRB could make a determination at a convened meeting that certain research at the institution or all research at the institution warrants continuing review and that determination could be documented in an institutional or IRB policy.

The rationale for why continuing review is required should be specific to the review of a particular study or group of studies. For example, a rationale that a study is using new or novel analytical techniques is an appropriate reason for why continuing review for a particular study or group of studies would be appropriate.[3]

[FN #3: It should be noted, however, that during the delay period [Ed. note: now concluded], IRBs are not required to document the rationale of why the IRB determined continuing review is required when the regulations do no[t] otherwise require such review.]

3. If an IRB determined that a study was nonexempt human subjects research under the pre-2018 Requirements, may an institution transition the study to the 2018 Requirements in order to take advantage of an exclusion from the definition of research or an expanded exemption?

Yes. The 2018 Requirements expand the categories of research eligible for exemption, and specify several categories of activities that are deemed 'not human subjects research' (by excluding these categories from the definition of research)**"** (guidance, January, pp. 13-14 of 17; on the Web at https://www.regulations.gov/docket?D=HHS-OPHS-2019-0001).

Timing of IRB Review Makes a Difference

"Institutions are permitted to transition research in order to take advantage of the explicit exclusion of certain categories of studies from the definition of research (beginning July 19, 2018), and the expanded exemption categories (beginning January 21, 2019).

4. Do the 2018 Requirements specify how an institution or IRB must ensure that a transitioned study complies with the 2018 Requirements on and after its transition date?

No. While an IRB does not need to revisit actions taken before a study's transition date, it must ensure that the study is complying with the appropriate requirements on and after the study's transition date.

As a matter of administrative convenience, an IRB or institution could consider reviewing studies for compliance with the 2018 Requirements before a study is officially transitioned, provided that the IRB's actions taken before the study's transition date are consistent with the pre-2018 Requirements.

Such actions taken before a study's transition date to ensure that a study will be conducted consistent with the 2018 Requirements need not be re-reviewed on and after a study's transition date.

C. Informed Consent

1. If a new consent is sought from already enrolled subjects in ongoing research that transitions to the 2018 Requirements, what standards must that consent meet?

All regulatory IRB actions that occur prior to an ongoing study's transition date (or prior to January 21, 2019 for studies that transition during the delay period) must comply with the pre-2018 Requirements ...**"** (supra at p. 14). © **{TBC}**

IRBs and Risk-Benefit Issues in Opioid Research Protocols - #1

As we've said more than once, the best time to influence a regulation is before it is a regulation. Hence, we devote this article to an ongoing federal discussion on what to do about the "Opioid Epidemic."

We do not focus on public policy or treatment/control of the involved substances, but on the research and human subjects issues important to IRBs.

This is due to the fact that, inevitably, research protocols are going to be submitted to IRBs for review if they haven't already. In such cases, the weighing of risk/benefit ratios in biomedical studies with human subjects may be even more challenging that with other less addictive drugs. This area is highly likely to become even more relevant in the future for IRBs and applicable researchers as well.

Due to the national interest in the overall topic, the FDA scheduled a September 17 public meeting in Silver Spring, Maryland, titled "Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction."

Benefit-Risk Assessments Are Key for IRBs and Researchers

Before proceeding with our discussion of the opioid research elements of most interest to IRBs, note that FDA will accept comments until November 18 on the numerous research factors that were planned for discussion at the September 17 meeting and will be considered for future FDA research requirements.

The contact person for said comments is FDA's Nicole Zelenak of the Center for Drug Evaluation Research at 301-796-9030, or send email to nicole.zelenak@fda.hhs.gov.

As can be seen in the following excerpt from the FDA's Federal Register announcement about the public meeting, "benefit-risk" assessments are at the heart of research issues surrounding development of drug alternatives to opioids. Traditionally, of course, such assessments are key to IRB reviews as well.

> **"I. Background**
>
> The 'Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (or SUPPORT for Patients and Communities Act) 1' was signed into law on October 24, 2018.
>
> One provision of this law requires FDA to hold not less than one public meeting to address the challenges and barriers of developing non-addictive medical products intended to treat acute or chronic pain or addiction, which may include the manner in which the risks of abuse or misuse of a controlled substance may be incorporated into the benefit-risk assessment for new drug approvals under section 505(d) and (e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d) and (e)).
>
> All opioids approved to treat pain are controlled substances. They are a crucial component of the armamentarium available for treatment of pain, but they carry serious risks of addiction, overdose, and death.
>
> Potent novel analgesics that do not carry these risks could significantly reduce or even obviate the need for opioid analgesics, but development of such drugs has remained elusive**"** (84 Fed. Reg. 29112-29114 at p. 29113, June 21).

Benefit-Risk Assessment Is Key to Federal Research Approvals As Well

> **"**FDA is optimistic that the enormous societal need, and the efforts of all stakeholders to meet that need, will drive scientific advances in the development of novel, safer analgesics.
>
> In the meantime, however, opioid analgesics are likely to remain a necessary part of medical practice despite their risks.
>
> FDA's goal is to regulate opioid analgesics in such a way as to reduce their serious risks to the greatest extent possible, while ensuring their continued availability to the patients who need them.
>
> Under our existing authorities, FDA determines whether each new drug application - including each new opioid drug application - meets applicable standards for safety and effectiveness.
>
> In applying these standards, FDA evaluates whether the benefits of the drug outweigh its risks. Benefit-risk assessment is the foundation of FDA's regulatory review of human drugs and biologics.
>
> It reflects the Agency's consideration of the evidence, identification of uncertainties, and the reasoning the Agency uses to make specific regulatory decisions, including product approvals.
>
> Additionally, the benefit-risk assessment for a particular medical product serves as a tool for communicating the Agency's findings about the product.
>
> FDA today issued a draft guidance on the application of FDA's benefit-risk assessment framework to applications for approval of opioid analgesic drugs entitled 'Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework - Guidance for Industry '**"** (ibid) [see the next article in this HRR issue]. **© {TBC}**

IRBs, Opioid Risk Issues, and New Research Protocols - #1

As described in the preceding article in this HRR, the national opioid crisis shows no sign of letting up. Similar to responses to health-related crises in the past, we can expect that interest in, and financial support for, more research projects will increase in response to the associated problems.

For IRBs faced with the responsibilities of reviewing research protocols in this area, special considerations are in order. As also described in the immediately preceding HRR article, a number of those special considerations are being addressed via a public FDA-hosted meeting and federal developments planned for the future.

However, FDA is not waiting for said developments. At the same time as the public meeting was announced, the FDA also released a new guidance for this special topic. The guidance is titled "Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework (June)."

Benefit-Risk Assessment Is Central Focus

"The purpose of this guidance is to describe the benefit-risk assessment framework that the Agency uses in evaluating whether applications for opioid analgesic drugs meet the standard for approval under section 505 of the Federal Food, Drug, and Cosmetic Act.

This guidance summarizes the information that should be included in a new drug application for an opioid analgesic drug to facilitate the Agency's benefit-risk assessment ....

Benefit-risk assessment is the foundation for FDA's regulatory review of human drugs and biologics. These assessments capture the evidence, uncertainties, and reasoning used by FDA to arrive at its regulatory decisions. Additionally, these assessments serve as tools for communicating that information to those interested in a better understanding of FDA's thinking ....

FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling. However, because of the widespread misuse and abuse of prescription opioid analgesic drugs, for this class of drugs, FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others.

Likewise, FDA considers any properties of a drug expected to mitigate these risks. This guidance describes the various factors that FDA will consider in evaluating the benefits and risks of an opioid analgesic drug. FDA encourages applicants to provide information relevant to these factors.

FDA has developed a benefit-risk assessment framework - a structured, qualitative approach to FDA's benefit-risk assessment[2] ....

[FN #2: See the *Enhancing Benefit-Risk Assessment in Regulatory Decision-Making* web page available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm ....] (guidance, pp. 1-2; on the Web at https://www.fda.gov/media/128150/download).

Research Efficacy Questions Posed By FDA

"III. BENEFIT-RISK ASSESSMENT

The following sections describe the information that FDA will consider in assessing the benefits and risks of an opioid analgesic drug. Consistent with the benefit-risk assessment framework, FDA considers the benefits and risks to the patient when the drug is used as labeled, as well as the benefits and risks relative to other available therapies for pain.

Additionally, FDA considers the public health risks of the drug related to misuse, abuse, opioid use disorder, accidental exposure, and overdose in both patients and nonpatients, as well as any properties of the drug that may mitigate such risks. Note that the risk of opioid use disorder can arise even when a patient is taking an opioid analgesic drug as labeled.

The sections below provide recommendations for information the applicant should provide to assist FDA in its assessment.

A. Benefits to the Patient Using the Drug as Labeled

The Agency will consider questions including the following about benefits to patients who are prescribed the drug and take it as labeled and directed by their prescribers:

- Analgesic efficacy of the drug when used for its proposed indication
  - 'What is the body of evidence supporting a finding of analgesic drug efficacy?'
  - 'In what patient population(s) was efficacy demonstrated?'
- Why was the patient population chosen for the efficacy study?

How does the population studied reflect the proposed indication (i.e., is the proposed indication broader than the population studied)?**"** (supra at p. 3). **© {TBC}**

IRBs and Research With Neonates - #1

Comments are due by October 30 on a new draft guidance issued by FDA that is titled "General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products." Although much of the guidance is directed towards basic science features of such studies, there are two reasons why we choose to present its highlights in the HRR.

First, the human subject population in this case is an especially vulnerable one. Thus, researchers who conduct applicable studies, and the IRBs that review the experiments' protocols, have special cautions and subject safety factors to consider.

Second, even the basic science factors addressed in the guidance matter to IRBs. Why? Because the details of the guidance's recommendations on such study parameters as dosage levels and sample sizes can have direct impacts on investigational product effectiveness. In turn, those parameters can have a direct impact on human subject safety.

For such reasons, IRBs are often cautioned not to focus exclusively on matters like informed consent (although consent is obviously crucial), but also on experimental design features that can affect the safety and welfare of human subjects as well.

A Special Group of Human Subjects

Before proceeding with highlights of this new guidance, note that the FDA contact persons for submitting comments or seeking additional information are Rajnikanth Madabushi of CDER at 301-796-1537 and CBER's Stephen Ripley at 240-402-7911.

> **"**This draft guidance is intended to assist sponsors [including researcher-sponsors] of new drug applications (NDAs), biologics license applications (BLAs) for therapeutic biologics, and supplements who are planning to conduct clinical studies in neonatal populations.
>
> The issuance of this draft guidance on clinical pharmacology considerations for neonatal studies for drugs and biological products is stipulated under the FDA Reauthorization Act of 2017 (FDARA) ....
>
> Given that most drugs used in Neonatal Intensive Care Units are used in an off-label capacity, studies of therapeutic products need to be conducted in neonates.
>
> In addition, therapies need to be developed for conditions unique to neonates. This draft guidance addresses:
>
> (1) Subgroup classification of neonates;
>
> (2) general pharmacokinetic, pharmacodynamic, and pharmacogenomic considerations for clinical pharmacology studies in neonates; and
>
> (3) clinical pharmacology considerations for any planned studies in neonates whether the studies are conducted pursuant to the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act, or neither.
>
> This draft guidance does not discuss the timing to initiate neonatal studies. Questions regarding the appropriate timing for the initiation of neonatal studies should be discussed with the relevant FDA review division**"** (84 Fed. Reg. 37653-37655 at p. 37654, August 1).

Specific recommendations on research design and methodology, as highlighted below, are the types of experimental features included throughout the guidance that are relevant for IRB consideration when reviewing applicable protocols.

A Population With Major Differences Between Subjects

> **"**During *in utero* development, there are significant physiological changes in the fetus involving the normal expression and maturation of organs and tissues including enzyme systems, receptors, transporters, and neurotransmitters.
>
> Once fetal development is interrupted by preterm delivery, the normal developmental trajectory of these systems is altered based on the physiological changes that occur after birth.
>
> Postnatal development can also be adversely affected by concurrent illnesses, resulting in altered maturation of organs and tissues and affecting the systems responsible for product absorption (A), distribution (D), metabolism (M), and excretion (E) (ADME).
>
> Gestational age (GA) at birth, postnatal age (PNA), and other factors (e.g. concurrent illness, underlying disease) can alter the pharmacokinetic (exposure) and pharmacodynamic (response) characteristics of a drug, which are essential components of the clinical pharmacology assessment.
>
> For example, a neonate born at 24 weeks gestation who is 4 weeks PNA is physiologically different compared to a 28-week gestation neonate who has just been born. The clinical pharmacology assessment should include a range of gestational ages, postnatal ages, and body weights, if feasible, unless the drug is intended to treat only a specific neonatal subpopulation**"** (guidance, July, p. 2 of 18; on the Web at https://www.fda.gov/media/129532/download). **© {TBC}**

IRBs and Fabry Disease Experiment Features - #1

Comments are due by November 6 on a new draft guidance titled "Fabry Disease: Developing Drugs for Treatment."

> "This draft guidance describes the Agency's current recommendations regarding eligibility criteria, trial design considerations, and efficacy endpoints to be used in clinical development programs of investigational drugs to treat Fabry disease" (84 Fed. Reg. 38994-38996 at p. 38995, August 8).

Since Fabry Disease (FD) is rare, we will not devote a significant amount of space in HRR to its ethical or regulatory features. However, for IRBs faced with reviewing applicable study protocols, a certain amount of attention is warranted.

Before proceeding, note that a contact person for more information, including advice on how to comment on the new guidance, is FDA's Jeannie Roule of CDER at 301-796-3993.

Male Research Subjects Most Likely at Risk

Since the biochemical bases for FD are complex, we shall leave such details to those researchers and IRBs most closely involved with relevant studies. However, we note that IRB decisions on subject selection and trial safety for the human subjects can vary widely and be influenced by numerous presenting symptoms of FD sufferers. The risks to FD patients are significant.

> "FD is characterized by chronic symptomatology (e.g., gastrointestinal symptoms, neuropathic symptoms including pain, hypohidrosis or anhidrosis), slowly progressive organ damage eventually leading to chronic renal disease and renal failure, cardiovascular disease (e.g., hypertrophic cardiomyopathy, heart failure, myocardial infarction, arrhythmias); cerebrovascular disease (strokes); and early mortality ....
>
> Despite its X-linked inheritance, FD affects both males and females, although to different degrees. In general, male patients with the classic subtype experience the most severe clinical manifestations, multi-organ disease, faster disease progression, and an earlier age of symptom onset compared to male patients with the late-onset subtype and to female patients ....
>
> Overall, the rate of disease progression is highly variable in male patients with late-onset FD and in female patients" (supra at pp. 2-3 of 7; on the Web at https://www.fda.gov/media/129690/download). © {TBC}

Human Subject Privacy and Confidentiality Certificates

Comments are due by October 14 on a proposal to change a portion of the requirements for submitting an application to get a Certificate of Confidentiality (CoC). This particular proposal comes from NIH, although all agencies in the Department of Health and Human Services (HHS) are authorized to issue CoCs by the Public Health Service Act (42 U.S.C. 241(d)). Agencies issue CoCs to authorize:

> "... researchers to protect the privacy of human research subjects by prohibiting them [i.e., the researchers] from releasing names and identifying characteristics of research participants to anyone not connected with the research, except in limited circumstances specified in the statute" (84 Fed. Reg. 40426-40427, Aug. 14).

Faster CoC Requesting System Is Proposed

> "At NIH, the issuance of CoCs has been delegated to the NIH OER in the NIH Office of the Director. NIH received 529 requests for CoCs from April 2017 through March 2018 and expects to receive approximately the same number of requests in subsequent years.
>
> The NIH has been using an online CoC system to review requests and issue CoCs since 2015. The current CoC request form includes 15 sections of information collection from research organizations.
>
> The streamlined NIH CoC electronic system [now being proposed by NIH] will have seven sections of structured or short text fields. The information provided will be used to determine eligibility for a CoC and to issue the CoC to the requesting organization.
>
> Eligible requesting organizations that provide legally binding affirmations that they will abide by the terms of the CoC would be issued a Certificate of Confidentiality. This system is expected to increase efficiency and reduce burden for both requestors and NIH staff who currently process these requests" (supra at p. 40427).

NIH is requesting approval from the Office of Management and Budget (OMB) for three years for these changes to the CoC system operated by NIH. NIH estimates that individuals/organizations seeking such CoCs incur no costs in doing so. NIH also estimates that it only takes 20 minutes to complete a CoC request.

The NIH contact person for this proposal is Dr. Pamela Reed Kearney of NIH's Division of Human Subjects Research at 301-402-2512, or send an email to NIH-CoC-Coordinator@mail.nih.gov. ©

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In Congress: Research Regulations & Ethics

NIH Announces Halt to Fetal Tissue Research, Claims Ethical Reasons - #2

As we presented last month, NIH has halted its funding for certain types of experiments involving the use of fetal tissue. In addition, NIH has established a number of new requirements for reviewing and conducting research involving fetal tissue that it will still support. What NIH is targeting for support withdrawal, of course, is human fetal tissue (aka "HFT") obtained from elective abortions.

Selective Congressional - and ultimately, financial and regulatory - support for fetal tissue research not involving HFT is the primary aim of the two bills we cited last month; namely, S. 2308 and H.R. 64. Both are titled "Patients First Act of 2019." The threefold purposes of both bills are to:

> **"**(1) intensify research that may result in improved understanding of or treatments for diseases and other adverse health conditions.
>
> (2) promote research and human clinical trials using stem cells that are ethically obtained and show evidence of providing clinical benefit for human patients; and
>
> (3) promote the derivation of pluripotent stem cell lines without the creation of human embryos for research purposes and without the destruction or discarding of, or risk of injury to, a human embryo ....
>
> **HUMAN STEM CELL RESEARCH AND THERAPY**
>
> (a) IN GENERAL. - The Secretary [of Health and Human Services] shall conduct and support basic and applied research to develop techniques for the isolation, derivation, production, testing, and human clinical use of stem cells that may result in improved understanding of, or treatments for, diseases and other adverse health conditions, including pluripotent stem cells that have the flexibility of embryonic stem cells (whether or not such pluripotent stem cells have an embryonic source), and prioritizing research with the greatest potential for near-term clinical benefit in human patients, provided that such isolation, derivation, production, testing, or use will not involve -
>
> (1) the creation of a human embryo for research purposes;
>
> (2) the destruction of or discarding of, or risk of injury to, a living human embryo; or
>
> (3) the use of any stem cell, the derivation or provision of which would be inconsistent with the standards under paragraph (1) or (2).
>
> (b) GUIDELINES. - Not later than 90 days after the date of the enactment of this section, the Secretary, after consultation with the Director of NIH, shall issue final guidelines implementing subsection (a) to ensure that any research (including any clinical trial) supported under subsection (a) -
>
> (1) is clearly consistent with the standards established in subsection (a) if conducted using human cells, as demonstrated by animal trials or other substantial evidence; and ..." (S. 2308, July 29, pp. 2-3).

Publicly Disclosing Research Applications

> **"**(2) is prioritized in terms of potential for near-term clinical benefit in human patients, as indicated by substantial evidence from basic research or by substantial clinical evidence, which may include -
>
> (A) evidence of improvement in one or more human patients suffering from illness or injury, as documented in reports by professional medical or scientific associations or in peer-reviewed medical or scientific literature; or
>
> (B) approval for use in human trials by the Food and Drug Administration.
>
> (c) DEFINITIONS. - In this section:
>
> (1) HUMAN EMBRYO. - The term 'human embryo' includes any organism, not protected as a human subject under part 46 of title 45, CODE OF FEDERAL REGULATIONS, as of the date of the enactment of this section, that is derived by fertilization, pathenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.
>
> (2) RISK OF INJURY. - The term 'risk of injury' means subjecting a human embryo to risk of injury or death greater than that allowed for research on fetuses in utero under section 46.204(b) of title 45, CODE OF FEDERAL REGULATIONS (or any successor regulation) or section 498 of this Act ....
>
> At the end of fiscal year 2019 and each subsequent fiscal year, the Secretary shall submit to Congress a report outlining the number of research proposals under section 409K that were peer reviewed, a summary and detailed list of all such research proposals that were not funded, and an explanation of why the proposals did not merit funding**"** (supra at pp. 3-5). **© {TBC}**

FDA Warning*

*See page 12 for HRR policy on investigative reporting

(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: California Physician (Part 2)
Warning Letter Date: March 29, 2016
Investigation Period: August 11-September 29, 2015
Noncompliance In: Numerous Failures to Follow Investigational Plan Using Experimental Drug for Thyroid Cancer

* * *

Researcher Ignores Own IRB-Approved Protocol

We continue in this article with our coverage of a Warning Letter issued following an FDA investigation that was conducted in late 2015.

Of the three areas of regulatory noncompliance uncovered by FDA, we resume our coverage by concluding FDA's findings regarding the first area of noncompliance; namely, the researcher's failure to follow his own IRB-approved research plan.

We shall also begin presenting key portions of the second noncompliance area on the researcher's vital documentation lapses.

"We [i.e., the FDA] acknowledge that the finding noted in Item 1.a. above (Subject L-36) and the AFP [alpha-fetoprotein] findings in Item 1.b. above (Subjects L-10, L-20, L-21, L-35, and H-67) [see last month's September HRR] were not included on the Form FDA 483 you received, and that therefore, your written response does not address these findings.

c. Between July 8, 2014, and February 17, 2015, you failed to conduct a CT and/or PET scan at any of the required time intervals (i.e., every 3 months) for Subject L-36.

In your October 6, 2015, written response to the Form FDA 483, you indicated that because ... [drug name redacted by FDA] is nontoxic, you did not see the need to follow the protocol strictly.

In addition, you stated that some subjects were noncompliant with the protocol instructions to have laboratory tests and CT scans performed.

You also indicated that for subjects who did not have thyroid carcinoma, TSH assessment was unnecessary; and that for all subjects, appropriate cancer markers were used instead (e.g., prostate-specific antigen (PSA) for subjects with prostate cancer).

You also stated that some subjects had CT scans every 4 months instead of every 3 months, and some subjects were followed by vaginal colposcopy in addition to pelvic and rectal ultrasound examinations, rather than by CT scan, PET scan, or both.

Your written response is inadequate because you must adhere to protocol-required assessments despite the presumed safety of the investigational drug, and study subjects' purported responses to it.**"**

Details Can Just Slow You Down

"Although you followed subjects with cancer-specific blood markers, the protocol requires all subjects to undergo the following laboratory tests: complete blood count, chemistry-7, chemistry-24, liver and renal function, carcinoembryonic antigen, cancer antigen 125, cancer antigen 153, cancer antigen 199, TSH, AFP, 'and other tumor markers.'

Further, you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.

Your failure to perform protocol-required laboratory tests and scans jeopardizes subject safety and welfare, and compromises the validity and integrity of the data collected at your site.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation (21 CFR 312.62(b)).

As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

Case histories include records demonstrating that subjects met protocol-specified inclusion and exclusion criteria. You failed to maintain adequate and accurate case histories that included these records. Specifically:

a. You failed to maintain study records demonstrating that Subjects L-10, L-21, L-26, and L-36 met the protocol-specified inclusion criterion of failure to be helped by two separate regimens of conventional radiation therapy and/or chemotherapy before study enrollment.**"** © {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 30)
Key Issue(s): Possible IRB failure to protect human subjects, lack of informed consent, negligence, and violation of personal privacy by school officials (including 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

"Clearly Established" Constitutional Right Is Crucial to Lawsuit By Former Research Subject

We continue here with the legal arguments made by the defending university, researchers, and school administrators who attacked the defending high schooler's claim that her constitutional rights had been violated when she was a reluctant research subject.

Resuming where we left off last month, we note that one defendants' argument was that there must be a "clearly established" constitutional right for the student to make such a claim.

That argument was cited in *Anderson v. Creighton*, 483 U.S. 635, 640 (1987) and further elaborated as follows:

> **"**This standard means that even if a constitutional right has been established generally, its application in a particular set of factual circumstances may *not* be sufficiently established to overcome a defendant's claim of qualified immunity.[15] *B.C. v. Plumas Unified School Dist.*, 192 F.3d 1260, 1267 (9th w. 1999) (finding that a police dog sniff of students at school was a search under the Fourth Amendment, but holding that it was not 'clearly established' under existing law that such conduct constituted a search).
>
> [FN #15: The 'clearly established' standard has also been interpreted to mean that, where a plaintiff seeks to establish liability for a *constitutional right*, whether the official(s) violated *some other* statute or regulation is irrelevant, especially where such statute or regulation provides no private right of action under 42 U.S.C. §1983. *Davis v. Sherer*, 468 U.S. 183, 194 & n.12.
>
> Defendants have show[n], *supra* at Section V(B) and (C), that they have violated no statutes or regulations as to which plaintiff has a private right of action.]**"** ("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. 24-25).

What Does "Clearly Established" Constitutional Violation Really Mean?

"Therefore, that certain conduct violates the constitution will be 'clearly established' if 'various courts have agreed that (such) conduct is a constitutional violation under facts not distinguishable in a fair way from the facts presented in the case at hand.' *Saucier*, 533 U.S. at 202.

Plaintiff cannot make the required showing of clear establishment in the present case.

First, plaintiff cannot show that there was a clearly established constitutional right to participate in interscholastic sports. See *infra*, at 20.

Second, plaintiff cannot show that she had a clearly established right to bodily integrity at all, let alone one that is separate and apart from her rights under the Fourth Amendment (as applied to the states through the Fourteenth Amendment). See *supra*, note 13; *Norman v. Lawrence Berkeley Laboratories*, 135 F.3d 1260, 1269 (9th Cir. 1993) ('we generally 'analyze (medical tests and examinations) under the rubric of (the Fourth) Amendment' ') (quoting *Yin v. California*, 95 F.3d 864, 871 & n. 12 (9th Cir. 1996).

Third, plaintiff cannot show that she has clearly established rights to either dignified treatment or informed consent in the context of a non-invasive behavioral study on drug testing required of student-athletes. *Robertson*, 2002 WL 535045, at *4, *Wright*, slip op. at 14.

Fourth, plaintiff cannot show that defendants' alleged conditioning of plaintiff's participation in interscholastic sports on her consent to participate in the Study was clearly established as conduct in violation of the Constitution.**"** © **{TBC}**

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

• **October 14-18, 2019**, in San Diego, California: **"Clinical Research/Clinical Science Course."** The course will be presented by the Society of Clinical Research Associates (SoCRA), with the meetings to be held at the Wyndham San Diego Bayside. Module 1 includes IRB guidelines and ethical issues in clinical trials. Module 2 includes basic science issues and genetic research. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633.

• **October 19-23, 2019,** in San Francisco, California: **"2019 Annual Meeting of SRA International."** This conference will be held by the Society of Research Administrators International (SRA), with the meetings to be held at the Hilton San Francisco. Contact: SRA International, 1560 Wilson Blvd., Suite 310, Arlington, VA 22209 at 703-741-0140, or fax to 703-741-0142, or send email to communications@srainternational.org, or see their Web site at www.srainternational.org.

• **October 27-30, 2019**, in Las Vegas, Nevada: **"MAGI's Clinical Research Conference - 2019 West."** This conference will be presented by MAGI (Model Agreements & Guidelines International), and cosponsored by many groups and companies. Meetings will be held at the Planet Hollywood Resort. Contact: Norman Goldfarb, Chairman, MAGI, 2249 1/2 Sutter Street, San Francisco, CA 94115 at 650-465-0119, or fax to 855-734-2366, or send an email to ngoldfarb@magiworld.org, or see their Internet Web site at www.magiworld.org.

• **November 4, 2019,** Interactive Web Seminar (1:00 PM - 2:30 PM Eastern): **"Informed Consent Procedure: Lessons Learned from Inspection Findings."** This Web-based seminar will be offered by Barnett International. Contact: Barnett Educational Services, 250 First Avenue, Suite 300, Needham, MA 02494 at 800-856-2556, or send a fax to 781-972-5441, or send an email to customer.service@barnettinternational.com.

• **November 7-8, 2019**, in Miami Beach, FL: **"Clinical Site Coordinator/Manager Workshop: GCP for Coordinators, Research Associates, Study Nurses, and Site Managers."** This conference will be presented by the Society of Clinical Research Associates (or SoCRA), with the meetings to be held at the Holiday Inn Miami Beach Oceanfront. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **November 13-14, 2019**, in Philadelphia, Pennsylvania: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP."** This conference will be presented by the Society of Clinical Research Associates (SoCRA), with meetings to be held at the Sheraton Philadelphia Downtown. Topics include how FDA conducts clinical trial site inspections, adverse event reporting requirements, and the duties/responsibilities of IRBs. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or send email to Office@SoCRA.org. ©

HRR Policy on Investigative Reporting:** Investigations that are no longer timely, but contain valuable continuing education information on human subjects protection, usually appear without identifiers, for privacy reasons. More recent investigation findings that are presented as a protection for potentially involved research subjects or others possibly at risk from the cited study(ies) usually appear with identifiers. Recent human subject protection incidents contain identifiers only if an allegation/inquiry/investigation about alleged research subject abuses/risks contains the views/arguments/findings/defenses/rebuttals of ***all involved parties. The exception to the aforementioned policy occurs when said parties have had the opportunity to publicly explain their positions, but have declined to do so. In such cases, in the interest of public safety, we present what applicable information is available.

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