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PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRBs and "Key Information" In Informed Consent - #6

We continue here with more recommendations on changes to informed consent that are currently under review by the federal Department of Health and Human Services (HHS). These recommendations, as usual, have been issued by the Secretary's Advisory Committee on Human Research Protections (SACHRP).

Last month in the HRR we presented a portion of SACHRP's responses to a series of questions on possible consent changes as posed by the federal Office for Human Research Protections (OHRP). These questions, in turn, are being submitted continuously to OHRP by IRBs around the country who are faced with numerous practical challenges in protecting human subjects in research.

In the present article, we present SACHRP's response to OHRP's sixth question below.

Length of Consent Forms Is Not the Crucial Issue

"*Question 6:*

Under what circumstances should key information presented up front be repeated in the core sections of the consent form (recognizing that there is no [regulatory] requirement that any such information that is already presented at the front of the consent form needs to be repeated elsewhere in the consent form)?

Response to Question 6:

The intent of the key information is to create more understandable consent forms, not to shorten or lengthen consent forms.

SACHRP supports efforts to decrease the length of informed consent documents to the extent that they promote readability and understanding.

However, SACHRP also notes that the new consent requirements at §46.116(a)(5)(i) are additive to the existing elements of consent, that additional elements of consent have also been introduced at §46.116(a)(9) and §46.116(b)(7) to (9), and that none of the currently existing elements of consent have been removed.

It is likely that the 'concise and focused presentation of the key information' will also add to the length of the consent form.

Therefore, SACHRP takes the position that information presented in the key information section need not be repeated in the subsequent

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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sections of the consent document unless that information is necessary to help ensure that the body of the consent remains understandable to the subject, consistent with the goals of §46.116(a)(5)(ii).

If repeating information assists subject understanding, then it should be done. If the key information summary contains all the information necessary to fulfill a required element of consent, there may be no reason to repeat this information. Stated more simply, brevity should not sacrifice clarity.

Appropriately placed statements or links that reference information contained in other sections of the consent document may help minimize repetition" ("Attachment C - New 'Key Information' Informed Consent Requirements," October 17, 2018, pp. 8-9 of 12; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-november-13-2018/index.html).

How Much Information Is Enough in Consent?

"For studies with simple designs, the consent form itself may be just a few pages, meeting the requirements for being clear and concise and also containing key information in an appropriate format.

SACHRP believes that this flexibility should be addressed in the agencies' [future] guidance on concise consent" (supra at p. 9).

In addition to the specific questions posed to it by OHRP, the SACHRP provided HHS with more recommendations on changes to informed consent. We recall that the primary focus of these recommendations on informed consent involves "key information."

This includes new "key information" that is garnered during the course of a study that may not have been available to the researcher (or to the human subjects) at the outset of the experiment.

One of the principal reasons for this concern is the fact that new "key information" may have an impact on the risk-benefit ratio so central to consent and to IRBs' assessment of subject safety.

This is especially crucial in experiments with FDA-regulated materials (i.e., drugs, devices, biologics, and combination products).

In its recommendations, SACHRP began its "additional general comments" on informed consent changes with a look at how "key information" should be presented to human subjects.

1. SACHRP recommends that OHRP (and the other agencies) confirm that there is compliance flexibility going forward, unless and until such time as there is agreement on how to appropriately select and provide key information.

OHRP should specifically state that diverging from the preamble suggestions of key information would not incur a compliance risk as long as the full consent document meets the requirements of the regulations.

This is critical to encourage the development of creative and potentially better approaches to presenting key information and to improvement of the consent form and process as a whole.

Otherwise, researchers and IRBs will be reluctant to deviate from current practices, erring on the side of 'more is better' to ensure compliance" (ibid).

Role of "Reasonable Person" Principle

"SACHRP believes that the changes to the consent form requirements, including but not limited to the addition of the key information summary, should lead to new ways of organizing and presenting the required elements of consent, and also lead to the inclusion of new information that is not a required element of consent as appropriate, in order to best facilitate informed decision making.

Writing the consent form should reflect both understanding of the protocol and ability to translate the protocol into information useful to potential subjects.

SACHRP recommends that appropriate resources should be dedicated to supporting better consent preparation and research and that the agencies should target both consent form authors and those individuals who obtain consent in guidance on this topic, and carefully consider how to disseminate the guidance to those individuals.

2. SACHRP believes that it is important to regard the key information summary as an opportunity to orient, guide, and assist potential subjects in the decision making process.

Therefore, the key information summary should frame the purpose and process of informed decision making from the subject's perspective.

The key information summary should not be regarded as a stand-alone document that provides the potential subject with sufficient information to decide whether or not to participate in the research, thus relegating the rest of the consent form to auxiliary information that provides additive detail.

3. SACHRP also recognizes that flexibility is inherent in the concept of the reasonable person as applied to informed decision making.

The reasonable person concept recognizes that it is impossible for researchers to determine what information every individual participant would consider helpful in deciding whether or not to participate.

Instead, it asks researchers to include what reasonable people in the same or similar circumstances would want to or need to know.

The use of the reasonable person standard to guide drafting of the consent form does not obviate the obligation to respond to the distinct circumstances, preferences, and needs of individual participants; the opportunity for each participant to ask questions that can take into account that person's own distinct medical history, background, values and personality remains an important part of the consent process" (supra at pp. 9-10).

Electronic Communications for Human Research Subjects

"**4.** SACHRP notes that e-consent and other formats for presenting consent information may make it easier to provide a concise and focused presentation of the key information, and also to organize and present the information in a way that facilitates comprehension and understanding of the reasons why one might or might not want to participate.

When e-consent is used, it will be much easier to use links to connect the information in the key information summary to more complete descriptions later in the consent form, as well as to video and audio presentations of content.

In addition, e-consent can use links to outside sources of information, such as websites and dictionaries. New approaches to presenting consent should be tried and assessed.

5. SACHRP recommends that empirical research should be conducted in light of implementation of the new consent requirements.

It will be important to determine whether and how different models of the concise summary of key information can best facilitate potential subjects' understanding, and to use those research results to improve the consent form and process.

The posting of consent forms in accord with new rule section §46.116(h) will provide source materials to use in such research" (supra at p. 10).

SACHRP Urges Research On Informed Consent Itself

"SACHRP encourages funding agencies to provide support for these research efforts, and such research should be generalizable and conducted on a large scale across sites, studies and populations.

The research should address both the best means to identify key information, and also how to present that key information to subjects in the consent form and process.

A gap in the current research on informed consent is an emphasis on what subjects want and need to know to make an informed decision.

Conclusion

The revised regulations include new requirements intended to improve the consent form and the consent process.

Under the new requirements, informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject in understanding the reasons he or she might or might not want to participate, and it must be organized and presented in a way that does not merely provide lists of isolated facts, and there must be an opportunity to discuss that information.

As a result, the Common Rule agencies and the regulated community have a significant opportunity to make the informed consent process better for research subjects.

SACHRP hopes that all involved parties will take full advantage of this opportunity and work together to advance the application of the ethical principle of respect for persons" (ibid). © {TBC}

IRBs and COVID Restrictions on Research and Study Protocols - #3

COVID-19 is continuing to change human subjects research in many ways, and to alter the operations of institutions and their IRBs that review such studies.

One effort designed to assist affected IRBs, researchers, and institutions is being spearheaded by the Council on Governmental Relations (or COGR).

We continue this month with a topic we introduced in the July HRR; namely, how institutions around the country are dealing with COVID impacts and how those experiences might help others involved in human subjects research.

The relevant new document by COGR is titled "Research Ethics & Compliance Committee - Human Subjects FAQs." The document uses a "Frequently Asked Questions" (FAQ) format to offer practical examples of how IRBs and others are addressing the many COVID-caused challenges for human research projects throughout the country.

When IRB Approval Can Be Waived

We continue here where we left off in the August HRR with the final portion of COGR's response to OHRP's Question number two as follows:

> **"2. How are institutions addressing the issue of continued recruitment to studies that are already underway?**
>
> **Answer:** .... [In addition to other steps, institutions] may permit recruitment for therapeutic research that is potentially 'life-saving' or 'disease altering' and for which there is no other alternative clinical treatment.
>
> Finally, many institutions permit the continued conduct of and recruitment into research in which both recruitment and the study itself can be safely and effectively conducted remotely without the need for in-person interaction. (See, e.g., HARVARD COVID-19 FAQs; Partners COVID-19 Human Research Policy).
>
> **3. How are institutions addressing the issue of patients who can no longer come to the institution for in-person protocol-required visits because of state and local COVID-19 related restrictions?**
>
> **Answer:** Study sponsors and investigators, in consultation with IRBs, are reviewing protocols to determine what alternative processes can be used to replace in-person interactions while still ensuring participant safety .... Investigators should review their particular IRB requirements to determine local requirements.
>
> For cases in which protocol modifications are required to eliminate in-person interactions (e.g., substituting phone visits for in-person visits), such changes may be made without prior IRB approval if they are necessary to eliminate 'apparent immediate hazards to the subjects'; however, these changes should be reported to the governing IRB as soon as possible (Office for Human Research Protections (OHRP) GUIDANCE ON COVID-19 ..., April 8, 2020 at [https://www.]hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.htm; FDA COVID-19 GUIDANCE page 7; 21 CFR 565.108; 45 CFR 46.108 (a)(3) & (4))" ("FAQs," May 4, Version 1.0, p. 2; on the Web at https://www.cogr.edu/sites/default/files/FAQS%20ON%20 HUMAN%20SUBJECTS%20for%20REC %20final%20may%204%202020.pdf).

Submitting One Type of Proposed Change to IRB First

> "Changes that are not related to removing harm or offering therapeutic benefit (e.g., omission of a safety lab that cannot be conducted remotely) should be submitted to the IRB in advance for review and approval.
>
> When protocol changes involve an investigational item under an investigational New Drug Application (IND) or investigational New Device Application (IDE), amendments also will be required to the IND or IDE ....
>
> In some cases, changes may not be required to the protocol as a whole, but rather some minor deviations may be necessary to accommodate a subject who cannot travel to the study site because of COVID-19 restrictions.
>
> In these cases, sponsor permission should be sought for such deviations, and sites may want to develop forms for this purpose.
>
> Additionally, the PI should carefully review protocol, clinical trial contract[,] and governing IRB policies to determine requirements for reporting such deviations to the IRB.
>
> Deviations that do not adversely affect data integrity or a subject's safety, welfare, or willingness to participate in the study may require reporting only at continuing review .... (21 CFR 56.108; ..." (supra at p. 3). © {TBC}

IRBs and Developing Drugs and Biologics During COVID-19 (#4)

We continue here with the FDA's recent advice to researchers and others (e.g., IRBs) on conducting most types of human research involving drugs and biological products related to COVID-19. The guidance is titled "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention" (see https://www.fda.gov/media/137926/download).

"This guidance is intended to remain in effect for the duration of the public health emergency related to COVID-19 declared by HHS, including any renewals made by the Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2).

However, the recommendations and processes described in the guidance are expected to assist the Agency more broadly in its continued efforts to assist sponsors in the clinical development of drugs for the treatment of COVID-19 beyond the termination of the COVID-19 public health emergency and reflect the Agency's current thinking on this issue" (85 Fed. Reg. 29949-29951 at p. 29951, May 19).

Appropriate Clinical Endpoints For Human Research Subjects

The guidance contains specific recommendations for researchers in their studies on COVID-19, and by implication for the IRBs that review such studies. For example, we continue here with the guidance's advice on "Efficacy Endpoints" to use in human subjects research.

"• Examples of important clinical outcome measures in treatment trials include the following:

-- All-cause mortality

-- Respiratory failure (i.e., need for mechanical ventilation, ECMO [extracorporeal membrane oxygenation], noninvasive ventilation, or high-flow nasal cannula oxygen delivery)

-- Need for invasive mechanical ventilation

-- Need for intensive care unit (ICU) level care based on clear definitions and specific clinical criteria

-- Need for hospitalization based on clear definitions and specific clinical criteria

-- Objective measures of sustained improvement (e.g., return to room air or baseline oxygen requirement)

-- Sustained clinical recovery (e.g., resolution of symptoms)

• The choice, time frame, and interpretation of endpoints may differ depending on the population evaluated in the trial. For example,

-- In a trial in severe and/or critical patients, examples of appropriate endpoints could be

- All-cause mortality at an appropriate time point (e.g., at least 28 days)

- Proportion of patients alive and free of respiratory failure at an appropriate time point (e.g., at 28 days)" (guidance, pp. 8-9).

Important Difference Between Phase 2 and Phase 3 Studies

"- Clinical status at an appropriate time point assessed using an ordinal scale[23] that incorporates multiple clinical outcomes of interest (e.g., death, mechanical ventilation) ordered by their clinical importance[24])

[FN #23: An example can be found in WHO R&D Blueprint novel Coronavirus, available at https://apps.who.int/iris/handle/10665/330695.

FN #24: Ordinal data should be collected daily to inform analyses.]

• Time to sustained recovery assessed over an appropriate duration

-- In an outpatient treatment trial, examples of appropriate endpoints could be

- Proportion of patients hospitalized by an appropriate time point (e.g., at least 28 days)

- Time to sustained clinical recovery assessed over an appropriate duration

• Sponsors should address potential relapses in their endpoint definitions to ensure adequate assessment of the durability of response.

• In phase 2 treatment trials, a virologic measure may be acceptable as a primary endpoint to support a phase 3 clinical endpoint study.

However, virologic endpoints are not appropriate as primary endpoints in a phase 3 trial because there is no established predictive relationship between magnitude and timing of viral reductions and the extent of clinical benefit of how a patient feels, functions, or survives" (supra at p. 9). © {TBC}

IRBs and COVID: Statistical Considerations in Studies - #2

We continue here with an area that we addressed last month that we do not often cover for IRBs and researchers. That area involves the use of statistics to help interpret the significance of experimental results in human studies.

The accuracy and appropriateness of whatever statistics a researcher might use has a direct bearing on the meaningfulness of his/her results.

By extension, the same characteristics of the statistics may impact whether or not any human subject risks were worth the subject's participation in a study.

Since the safety and well-being of subjects are paramount responsibilities of IRBs, the area of statistics therefore is relevant for IRBs.

Hence, in this COVID crisis, the FDA has issued a new guidance titled "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency."

We pick up where we left off last month with more FDA recommendations from the guidance's section titled "B. Trial Mitigation and Analysis Strategies," as follows below.

Statistics and the Effects of Subject Enrollment Changes Due to COVID-19

"(3) Stopping a trial earlier than planned or adding interim analyses to the trial may impact the statistical inference (e.g., p-value, confidence intervals).

As stated above [see last month's HRR], any modification to the trial, including the original planned analyses, should not be based on data that reveal information on the treatment effect.

(a) If a trial had no previous interim analyses and is stopped early, then using the originally planned statistical analysis may be appropriate for the statistical inference.

The actual results may be less statistically significant or have a wider confidence interval than the trial was designed for because of reduced information (e.g., fewer endpoint events).

(b) If a trial had no previous interim analyses, it may be possible to add a plan for interim analyses.

(c) For a trial with a prospectively specified interim analysis plan, it may be possible to stop the trial earlier than planned or to add or modify an interim analysis and still maintain control over Type 1 error.

(4) A sponsor can consider increasing enrollment after the impact of COVID-19 has passed, as appropriate, over the originally planned enrollment to overcome the loss of information from the impact of COVID-19.

Similarly, a sponsor can consider extending follow-up to attain more events in an event driven trial.

Sponsors should conduct sensitivity analyses examining differences in baseline characteristics and post-baseline events (including endpoints and adverse events) between the originally enrolled participants and the additional participants to understand the impact of the change in recruitment, including changes to recruitment locations and time of recruitment" (guidance, June, p. 4; on the Web at https://www.fda.gov/media/139145/download).

What to Do About Missing Data Effects Due to COVID-19

"(5) Sponsors should consider how to approach the analysis of data from participants who are missing endpoint ascertainment or the investigational product was interrupted because of COVID-19.

(a) For a trial with sites closed for a period of time because of COVID-19, the missing endpoint ascertainments during this period may not necessarily be related to the treatment assignment or participant characteristics and outcomes.

In this case, removing all participants from closed sites who were scheduled for an endpoint ascertainment from the analysis should not bias the findings.

However, to avoid bias when using this approach, it is important to remove all the participants from the closed sites who were scheduled for the ascertainment, regardless of whether they had previously withdrawn -- e.g., one should not impute values for those who would have had the endpoint ascertainment impacted by COVID-19 had they remained in the trial.

For this approach, the exclusion of participants should not use post-baseline participant information but instead use only information at randomization" (supra at pp. 4-5). © {TBC}

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IRBs and FDA's Advice on How To Cope With Coronavirus - #3

The FDA continues to publish specific guidances for IRBs and researchers on ways to cope with COVID-19. Such guidances often focus on a single topic. However, the reality is that there are many COVID-related research issues that apply to many different types of studies.

For example, as we introduced in the May HRR, a new guidance for research on medical devices involving human subjects was released by FDA in March of this year. More recently, in July, that same FDA guidance was significantly expanded.

We resume below with our presentation of highlights from this FDA's guidance titled "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards."

Human Subject Retention Is Major Problem

As we saw in our June HRR, one set of problems faced by researchers, and the IRBs that review their studies, is keeping up with subject retention challenges such as revised visit schedules, missed visits, and even patient dropouts due to COVID-related transportation interruptions.

"• If scheduled visits at clinical sites will be significantly impacted, certain investigational products, such as those that are typically distributed for self-administration, may be amenable to alternative secure delivery methods.

For other investigational products that are normally administered in a health care setting, consulting FDA review divisions on plans for alternative administration (e.g., home nursing or alternative sites by trained but non-study personnel) is recommended.

In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.

• With respect to efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible.

For individual instances where efficacy endpoints are not collected, the reasons for failing to obtain the efficacy assessment should be documented (e.g., identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).

• If changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsor should consider doing so in consultation with the applicable FDA review division.

Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the prespecified analyses" (guidance, March, rev. July 2, pp. 7-8; see https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency).

Protecting Human Subjects Remains Paramount in Studies

"• If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites.

B. In general, and if policies and procedures are not already in place for applicable trials:

• Sponsors, clinical investigators, and IRBs should consider establishing and implementing policy and procedures, or revise existing policy and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites.

Changes to policy and procedures could address, but not be limited to, impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigator(s), site staff, and/or monitor(s) secondary to travel restrictions, quarantine measures, or COVID-19 illness itself.

Policy and procedures should be compliant with applicable (regional or national) policy for the management and control of COVID-19. Depending upon the nature of the changes described above, a protocol amendment may be required under the applicable regulations" (supra at p. 8). © {TBC}

IRBs, Human Subjects, and Study Data Confidentiality (#1)

The privacy rights of human subjects, especially the confidentiality of data about them, has long been a major concern for researchers and the IRBs that review human studies. An ongoing effort by the National Institutes of Health (NIH) is designed to enhance the ability of researchers and others to share such human subject data while still protecting data confidentiality.

NIH is currently reviewing the public comments it received following NIH's issuance of its "Draft NIH Policy for Data Management and Sharing and Supplemental Draft Guidance."

One group keenly interested in that NIH draft is especially concerned over what this may mean for human subjects research and concomitant human subject protections.

That group is the Secretary's Advisory Committee on Human Research Protections (SACHRP). On August 12 the SACHRP submitted its recommendations on the NIH proposal to Alex Azar, the current Secretary of Health and Human Services. Those recommendations contain much that will interest IRBs, including new recommendations on informed consent that could impact IRB protocol reviews.

IRBs Would Have to Review New "Data Management and Sharing Plan"

The SACHRP's views on the NIH proposal make it clear that, if enacted as originally released, the NIH policy changes will certainly affect researchers, IRBs, and anyone involved with human subjects studies.

> "The Draft NIH Policy for Data Management and Sharing and Supplemental Draft Guidance was released in November 2019, as a means to share broadly data from research funded or conducted by NIH and encourage good data management practices. The Policy seeks to encourage the broad sharing of scientific data with the research community and the public.[1]
>
> [FN #1: 84 Fed. Reg. 60,400 (Nov. 8, 2019).]
>
> Central to the Policy is a requirement that investigators of all research that generates scientific data and is funded or conducted by NIH prospectively submit a Data Management and Sharing Plan ('Plan') prior to initiating the study.[2]
>
> [FN #2: ibid.]
>
> The Plan must describe, in two or fewer pages, how scientific data will be managed, including strategies on how to ensure data security and compliance with privacy protections. Plans must be submitted to the funding NIH Institutes, Centers, and Offices (ICOs) as part of the funding application process (e.g., as part of Just-in-Time for extramural awards or technical evaluation for contracts).[3]
>
> [FN #3: ibid.]
>
> Plans are to be reviewed by appropriate NIH staff and ultimately become a term and condition of the relevant NIH award with which awardees must comply.[4]
>
> [FN #4: supra at p. 60,401.]" (in section titled "I. Data-Sharing Provisions in the Draft Policy as Applied to Human Participants" of "Attachment A - NIH Data Sharing Policy," SACHRP letter to Alex Azar, August 12; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/august-12-2020-attachment-a-nih-data-sharing-policy/index.html).

Failure to Follow Plan Could Lead to Loss of Research Funding

> "Failure to comply with a submitted Plan may result in an enforcement action, which can include the imposition of additional special terms and conditions or termination of the award. In addition, failure to comply with the Plan may have an effect on future funding decisions.[5]
>
> [FN #5: ibid.]
>
> NIH states that the Policy was intentionally kept at a high level to allow for flexibility across various scientific domains.[6]
>
> [FN #6: supra at 60,399.]
>
> In recognition of the generality of the Policy, NIH has also released supplemental draft guidance on (1) allowable costs for data management and sharing and (2) elements of an NIH data management and sharing plan.
>
> With respect to human participants, the Policy recognizes that the sharing of data derived from such individuals should be afforded additional protections, and the sharing of human participants' data is governed by applicable federal, tribal, state, and local laws, regulations, statutes, guidance, and institutional policies, whose restrictions all investigators must accommodate in any Plans.[7]
>
> [FN #7: supra at page 60,401.]" (ibid).

Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** Comments are being accepted ***until October 13*** on a proposed information collection consisting of required reporting to FDA and record keeping by affecting entities. This activity is part of FDA's efforts to get an extension of current approval from the Office of Management and Budget (OMB) for FDA's requirements regarding ***"Medical Devices: Humanitarian Use Devices"*** (OMB No. 0910-0332).

> "Respondents may submit a humanitarian device exemption (HDE) application ***seeking exemption from the effectiveness requirements*** of sections 514 and 515 of the FD&C Act .... The information collected will assist FDA in making determinations on the following: (1) Whether to grant HUD designation of a medical device; (2) whether to ***exempt an HUD from the effectiveness requirements*** ..., provided that the device meets requirements as set forth under section 520(m) of the FD&C Act; and (3) whether to grant marketing approval for the HUD" (85 Fed. Reg. 49379-49381 at p. 49380, August 11).

For more information, contact: Ila S. Mizrachi at 301-796-7726.

• **Food and Drug Administration.** Comments are being accepted on a new final guidance titled "Clinical Investigations for Prostate Tissue Ablation Devices." This guidance contains ***recommendations for IRBs and researchers*** for the referenced type of studies.

> "This guidance provides recommendations for clinical investigations for high intensity ultrasound systems for prostate tissue ablation and new types of prostatic tissue ablation devices ....
>
> The scope of this guidance is limited to the clinical investigations of prostate tissue ablation systems to support marketing authorization for a general indication for ablation of prostatic tissue" (85 Fed. Reg. 42858-42860 at p. 42859, July 15).

The guidance itself contains a number of specific recommendations for affected entities. For example, in the guidance's section titled "IV. Clinical Investigation Recommendations," FDA states that:

> "Generally, we believe prostate tissue ablation devices addressed by this guidance document are significant risk devices subject to all requirements of the Investigational Device Exemption (IDE) regulation, 21 CFR 812, for studies conducted in the United States (US).
>
> See the FDA guidance titled, 'Significant Risk and Nonsignificant Risk Medical Device Studies.[3]
>
> [FN #3: [See] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.]
>
> In addition to the requirements of 21 CFR 812, sponsors of such trials of a device conducted in the US ***must comply with the regulations governing institutional review boards (21 CFR 56) and informed consent (21 CFR 50)"*** (guidance, July 15, p. 2; see https://www.fda.gov/media/128263/download).

For more information, contact: John Baxley of FDA's CDRH at 301-796-6549.

• **Food and Drug Administration.** Comments are being accepted on a new draft guidance titled "Drug-Drug Interaction Assessment for Therapeutic Proteins."

> "The purpose of this guidance is to provide a systematic risk-based approach to help sponsors of investigational new drug applications (INDs) and applicants of biologics license applications (BLAs) determine the need for drug-drug interaction (DDI) studies for a therapeutic protein (TP)" (85 Fed. Reg. 48259-48261 at p. 48260, August 10).

Although much of this guidance is devoted to discussions of biochemistry, portions dealing with experimental design are ***relevant for IRB consideration***. This is due to the fact that appropriate design can affect the adequacy of study results which, in turn, can ***justify (or not justify) the level of risk exposure for human subjects***. Design can also influence ***enrollment of the human subjects***.

> "Clinical studies of TPs should consider the suspected mechanism for the DDI ***when selecting the relevant study population*** and the interacting drugs to evaluate. The study design (parallel or crossover) should be informed by the suspected mechanism of the DDI and the pharmacokinetic (PK) characteristics of the drugs ...." (guidance, August, p. 5; on the Web at https://www.fda.gov/media/140909/download).

For more information, contact: Elimika Pfuma Fletcher of FDA's CDER at 301-796-3473. ©

FDA Warning

Warning Letter To: Texas Physician (Part 3)
Warning Letter Date: June 28, 2016
Investigation Period: February 1-18, 2016
Noncompliance: Failing to Follow Approved Research Plan

* * *

Researcher's Defense Falls Flat Without Action Plan for Corrections

We now conclude our coverage of this FDA investigation. Last month we presented the final portions of the investigator's findings on the researcher's failure to follow approved dosage levels for the experimental drug. We continue here with the FDA's additional conclusion that:

"We are unable to undertake an informed evaluation of your written response because you did not provide a corrective action plan that, if properly carried out, would prevent this type of violation in the future.

Specifically, you did not provide sufficient details on how you will ensure adherence to protocol-specific requirements for other future studies.

2. -- The protocol states that since ... [redacted by FDA] is cleared primarily through the kidneys, a dose adjustment is required for reduced renal function. If the eGFR drops to <30 mL/min/1.73m^2, based on two consecutive serum creatinine determinations, the ... [redacted by FDA] dose will be reduced to 25 mg once daily.

The protocol specifies that the most recent available serum creatinine and eGFR values should be obtained as part of usual care at Annual and Brief Visits, and that study investigators will down-titrate the dose of blinded study medication if renal function deteriorates based on the most recently available serum creatinine/derived eGFR.

If a dose adjustment is needed, the subject will be brought in for an unscheduled visit (unless a scheduled visit is planned within one month), and the dose adjustment managed through the Interactive Voice Response System (IVRS).

Despite two consecutive eGFR values < 30 mL/min/1.73m^2 for Subject 112194, you failed to down titrate study drug as required by the protocol ....

Despite this subject having two consecutive eGFR values <30 mL/min/1.73m^2 , you did not down titrate Subject 112194 to 25 mg of study drug at the Month 18 Visit as required by the protocol. Study records indicate that Subject 112194 was still taking 50 mg of study drug at the Month 21 Visit that occurred on December 3, 2013."

Researcher "Jeopardized Subject Safety"

"In your March 4, 2016, written response to the Form FDA 483, you indicate that Subject 112194 was seeing his nephrologist during the study. The nephrologist ordered labs for this subject with the following eGFR values:

- March 23, 2012 (randomization/Visit 1) – 49 mL/min/1.73 m^2
- July 23, 2012 (Month 4/Visit 2) – 43 mL/min/1.73 m^2
- November 27, 2012 (Month 8/Visit 3) – 39 mL/min/1.73 m^2
- March 26, 2013 (Month 12) – 22 mL/min/1.73 m^2

You state that at the Month 18 Visit on September 19, 2013, the subject confirmed that his nephrologist ordered labs and after the visit, you requested the laboratory results from the nephrologist. Upon receiving the laboratory results several weeks later, you noted that the eGFR was 23 mL/min/1.73 m^2, which met the protocol criteria for down-titration of study drug.

You explain that you were not able to contact the subject to come in for down-titration of study drug, and that the subject withdrew from the study on January 15, 2014, prior to being down-titrated.

We are unable to undertake an informed evaluation of your written response because you did not provide a corrective action plan that, if properly carried out, would prevent this type of violation in the future ....

... [We find that] your failure to delay randomization for subjects who did not have serum creatinine by the end of Visit 1 and your failure to reduce the dose of study drug based on a drop in eGFR to less than 30 mL/min/1.73m^2 (based on two consecutive serum creatinine determinations), jeopardized subject safety and welfare, and compromised the interpretability of the data collected at your site." ©

In Court

Case: Amy Cordy, et al., v. Oregon Health and Science University (OHSU); aka Wade v. OHSU (Part 42)
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

* * *

Defendants Say Former Research Subject Was Only "Incidental Party" to Federal Agreement

We continue here with more of the arguments by the defending university, researchers, and IRB against the former research subject's lawsuit claims. We resume with why the defendants claimed that the former subject was not a bona fide "third party" to the university's human subject protection Assurance Agreement with the federal government.

Citing a previous case (*Klamath Water Users Protective Assoc. v. Patterson*), the defendants said that the high school student was not a "third party" and instead was only an "incidental party" who had no rights under the Assurance Agreement on protecting human subjects. *Klamath* involved:

> "(... a contract between the U.S. Bureau of Reclamation and the California Oregon Power Company governing the management of Link River Dam in the Klamath Basin, that irrigators in the Klamath Basin were only incidental beneficiaries to the contract, where the contract did not express a clear intention to grant irrigators enforceable rights thereunder).
>
> Here, there is no clear intent to grant enforceable rights to plaintiff, and plaintiff's claim must therefore fail**.**
>
> The purpose of the Assurance Agreement was to comply with DHHS regulations requiring the assurance of compliance as a condition precedent of federal funding of research involving human subjects.
>
> As a necessary consequence of its assurances, OHSU agreed to conduct its research in a manner that would ultimately benefit all human subjects participating in research carried out by OHSU, including plaintiff; however, there is nothing in the plain language of the Assurance Agreement that shows it was made for the 'direct benefit' of plaintiff. [See] *Klamath Water Users*, 204 F.3d at 1210, 1212 ('the recitation of constituencies whose interest bear on a government contract does not grant these incidental beneficiaries enforceable rights')" ("Memorandum in Support of Defendants ...," November 4, 2002, Docket Document #20, pp. 39-40).

Other Lawsuit Decisions Also Said "Incidental Parties" Do Not Have Special Contract Rights

> "*Wright*, supra [see previous HRRs] is directly on point. There, the plaintiffs, relatives of deceased patients who had participated in clinical trials involving bone marrow transplants performed at one defendant's facility, brought numerous claims against that defendant and others, including a claim for Breach of the Assurance Agreement.
>
> The substance of the allegations regarding the alleged breach of the Assurance Agreement in the *Wright* complaint is precisely the same as that in plaintiff's Fourth Claim for Relief ....
>
> The court in *Wright* dismissed the plaintiff's claim, holding that 'while human subjects of research conducted at the (Fred Hutchinson Cancer Research Center) would clearly benefit from defendants' compliance with the Assurance Agreement, plaintiffs have not identified any language in or provision of the Agreement that provides subjects with an actionable right, a fact which is sufficient to rebut the contention that plaintiffs are intended beneficiaries' ....
>
> The same conclusion is warranted in this case.
>
> The *Wright* decision is in line with other federal cases on this issue. Indeed, the Assurance Agreement is similar to assurances of compliance required as a condition of federal funding under *other* federal laws, and cases analyzing contract claims based on those assurances have found that they do not create enforceable rights to third parties. See, e.g., *Allstate Transportation Company, Inc. v. Southeastern Pennsylvania Transportation Authority* ... Mar. 27, 2000) ...." (supra at pp. 40-41).

© {TBC}

 See p. 12 for details.

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.

• **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 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.

• **November 2-12, 2020, v**irtual conference: **"MAGI's Clinical Research Conference."** Conference will be presented by MAGI (Model Agreements & Guidelines International). The 90+ workshops and sessions over multiple topic tracks include: good clinical practice and inspection readiness, regulatory compliance for human subjects research, informed consent, and subject injury. Contact: Norman Goldfarb, Chairman, MAGI, at 650-465-0119, or send email to ngoldfarb@magiworld.org.

• **November 12-13, 2020**, live virtual conference: **"Clinical Site Coordinator/Manager and GCP Workshop."** The topics will include: elements of informed consent, the reporting requirements involving Institutional Review Boards (IRBs) and Institutional Ethics Committees (IECs), and how to submit a protocol to an IRB. Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org.

• **November 18-19, 2020**, at the Wyndham Lake Buena Vista Disney Springs Resort in Orlando, Florida: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP."** Topics include: informed consent, how FDA performs inspections of clinical investigators, and the duties and responsibilities of Institutional Review Boards (IRBs). Contact: Conference Registrar, SoCRA, at 800-762-7292, or send email to Office@SoCRA.org.

• **December 1-4, 2020**, live virtual conference: **"Clinical Research Monitoring and GCP Workshop for Monitors, Site Coordinators, and Auditor."** Topics include: obligations of sponsors and monitors as required by the Food and Drug Administration, 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. ©

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