America's Oldest National Monthly IRB Newsletter

Human Research Report

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

Volume 38, No. 11 ISSN 0885-0615 November, 2023

This newsletter is copyright protected and sold with a limited license. See p. 12 for details.

Alert for All U.S.-Based IRBs! Can You Prove You're Actually Doing Your Job? (#3)

As we first described in September's HRR, the influential Secretary's Advisory Committee on Human Research Protections (SACHRP) is studying proposals about evaluating IRB effectiveness. These proposals were issued by the Government Accountability Office (GAO) earlier this year.

That GAO report is titled "Institutional Review Boards: Actions Needed to Improve Federal Oversight and Examine Effectiveness" (see https://www.gao.gov/assets/gao-23-104721.pdf).

We now believe even more strongly that this GAO report, and the SACHRP's recent recommendations based on that report, will revolutionize IRB operations in the United States.

The only questions for IRBs are "how much will change and when will the new rules be issued?"

How to Measure IRB Effectiveness?

However, this is unlikely to be an overnight event. Federal bodies are now discussing methods for ways to measure IRB effectiveness.

Once that phase is over, given current federal budget and accountability pressures on funding sources for IRBs, we can expect assessments of selected IRBs to begin around the country.

We resume our coverage of key developments in this new phenomenon with the main areas that SACHRP members are now examining.

"(SACHRP members, in regard to these proposed standards, please consider:

- Whether these are the appropriate [IRB] standards or whether we have missed some,
- Whether we should lower the number of proposed standards that are presented,
- The order in which these standards are presented [and],
- Which standard(s) you think are the best for the government to pursue)

For each of the proposed standards of measuring IRB effectiveness[,] comments are organized as follows:

- Pros
- Cons
- Feasibility for Government to enact
- Measurability
- Assessment of whether [the standards are] more administrative/procedural or [contain] more substantive ethics. For instance,

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

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

Also In This Issue

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

turn around time is an administrative measure, whereas ensuring participant autonomy is substantive. [and]

• IRB[-]Focused or [have a] broader focus including other parts of an HRPP [Human Research Protection Program]" (SACHRP Recommendation on GAO-23-104721, SACHRP draft Minutes, lines 113-127; on the Web via regulations.gov; enter HHS-OASH-2023-0012; then scroll down to GAO SACHRP Recommendation 7.12.23).

Are These the Relevant Standards for IRBs?

"(SACHRP members, please consider whether these are the appropriate points to consider for each of the proposed standards.

For instance, there is some overlap between the pros and cons and the other points.

Suggestions from the sub committees included:

- Get rid of pros and cons
- Add a column for Surrogate measure versus Direct measure
- Add an overall score column to the visual assessment diagram.

These same questions are on the separate visual assessment of the proposed standards)" (supra at lines 128-137).

Components of Separate IRB Effectiveness Measures

"**Possible Standards of IRB Effectiveness**

Compliance with the Belmont Principles

The first standard we propose is compliance with the principles put forth in the BELMONT REPORT.

The REPORT elucidates three ethical principles, [i.e.,] respect for persons, beneficence[,] and justice, that can be used to assess and guide the ethical conduct of research.

However, the principles themselves, even with their elaboration in the BELMONT REPORT itself and in much subsequent bioethics literature, are general in nature and can conflict with one another in the ethical assessment of a given research project.

For instance, the principle of justice can be interpreted to require the translation of a consent form into all local languages to ensure equitable enrollment, but if the investigator and staff do not speak these languages, then it can be seen as a violation of respect for persons to have a consent process between an investigator and subjects who do not share the same language.

In addition, the Common Rule was intended to incorporate the BELMONT principles into a comprehensive and enforceable regulation, and as such, compliance with the Common Rule may allow us to assess an IRB's adherence to the BELMONT Principles in a quantitative way" (supra at lines 139-152).

Details of the First Proposed Standard of IRB Effectiveness

"*Pros* [of the first 'Compliance with the BELMONT Principles' standard]

Directly ties to guiding document for providing ethical review of the conduct of research in the US

Cons

Principles are very high level, need interpretation based on facts

The introduction to a recent training course offered by PRIM&R [Public Responsibility in Medicine & Research] shows the complexity of the issues that need to be resolved by the application of the principles:

> Potential topics include ethical justification for randomized clinical trials; use of placebo; fCOI [Financial Conflict of Interest]; inclusion (and exclusion) of vulnerable subjects; phase 1 trials and risk-benefit analysis; compensation (and coercion) of subjects; optimizing informed consent; secondary research findings; data and safety monitoring; and assessment and minimization of risk. [see] *https://www.pathlms.com/primr/webinars/35483*, accessed 5/30/2023 ....

The IRB system is designed to have convened meetings of qualified individuals consider each protocol individually, and under that structure, different IRBs may make differing decisions on the same protocol.

Measuring the effectiveness of this process is therefore difficult. The principles provide the framework for ethical review, but the application is very nuanced and fact specific" (supra at lines 153-218 with omissions). © **{TBC}**

This newsletter is copyright protected and sold with a limited license. See p. 12 for details.

IRBs Have New Consent Procedures to Review (#2)

As we introduced in last month's lead article, the FDA has issued an extensive new guidance for IRBs and others on informed consent. Titled "Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors," the final guidance adds new advice for the research compliance community.

In addition to the section on human subject "coercion and undue influence" that we presented before, we now focus on FDA's guidance for IRB reviews of possible financial relationships and related factors.

"The clinical investigator should consider whether information related to financial relationships or interests should be provided to subjects.[66]

[FN #66: See the HHS guidance document, 'Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection,' available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/financial-conflict-of-interest/index.html#.]

Clinical investigators should consider the potential effects that a financial relationship might have on the clinical investigation or on interactions with subjects" (guidance, August, p. 37 of 61; on the Web at https://www.fda.gov/media/88915/download).

IRBs Have the Final Review Responsibility

"When there are financial relationships or interests, clinical investigators should consider the following actions:

• Including information in the informed consent form, such as:

– The source of funding and funding arrangements for the conduct and review of the clinical investigation, or

– Information about a financial arrangement or interest (e.g., stock in the study sponsor, patent on the investigational product) of an institution or an investigator and how it is being managed.

• Using special measures to modify the informed consent process when a potential or actual financial conflict exists, such as:

– Having another individual who does not have a potential or actual conflict of interest involved in the consent process, especially when a potential or actual conflict of interest could influence the tone, presentation, or type of information presented during the consent process.

– Using independent monitoring of the consent process.

Although the clinical investigator should consider these issues regarding financial relationships and interests, IRBs have the final responsibility of determining whether subjects should be provided with information regarding the source of funding, funding arrangements, or financial interests of parties involved in the clinical investigation as part of the informed consent process (see 21 CFR 56.109 and 56.111(a)(4)-(5))" (ibid).

Additional advice to IRBs and researchers on human subject communications appears in the guidance's section titled "**IV**. Responsibilities for Informed Consent, **A**. The IRB, **1**. Review of All Informed Consent Materials." For example:

"IRBs must review all materials used in the informed consent process (see 21 CFR 56.109(a)-(b) and 56.111(a)(4)-(5)). This includes recruitment materials[55], such as advertisements, and information provided in addition to the informed consent form (for example, a chart explaining what to expect at each study visit or a document explaining the costs to subjects)" (guidance, page 30).

Key Information Must Be Submitted to the IRB

"[FN #55: As described in the FDA Information Sheet 'Recruiting Study Subjects' (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recruiting-study-subjects), FDA considers advertising, including but not necessarily limited to newspaper, radio, TV, bulletin boards, posters, flyers, and internet postings, to be part of the consent process.

However, FDA does not consider listings of basic information about clinical investigations to be advertising for recruitment. We consider basic information to be information such as the title of the clinical investigation, purpose of the clinical investigation, protocol summary, basic eligibility criteria, investigational site locations, and how to contact the site for further information ....

Any posting about a clinical investigation where the format limits the information provided to basic information does not need to be reviewed by the IRB.

However, a posting that provides more than basic information should be submitted for IRB review.]" (ibid). © **{TBC}**

IRB Reviews During Public Health Emergencies (#1)

The impacts of the COVID pandemic upon human subjects research have been profound and widespread.

In recognition of this, FDA has issued its final guidance titled "Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies [PHEs]."

This guidance lists IRBs as a specific audience for its recommendations.

"FDA is issuing this guidance to provide general considerations to assist sponsors, institutional review boards (IRBs), and clinical investigators in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during disasters and PHEs that may lead to major disruptions of clinical trial conduct and operations" (guidance, September, p. 1; on the Web at https://www.fda.gov/media/172258/download).

Safety of Human Subjects Remains Paramount

"The final guidance provides recommendations for helping to address those challenges, including, among other things, recommendations related to the safety of trial participants, whether to continue or suspend a trial, protocol amendments and deviations, study monitoring, alternative delivery of the investigational product, remote safety and endpoint assessment, informed consent, and reporting of adverse events.

Some of the recommendations in this final guidance provide less burdensome approaches that can be utilized, when appropriate, in the conduct of clinical trials during major disruptions due to a disaster or PHE and that are consistent with public health.

For example, the guidance provides recommendations regarding a change to virtual, rather than in-person, clinical trial visits when necessary" (88 Fed. Reg. 65178, September 21).

Before proceeding with our highlight excerpts from the guidance itself, note that the FEDERAL REGISTER notice announcing this new guidance lists FDA's Dat Doan as the CDER contact person for more information about the guidance (Tel: 301-796-2500; or send email to CDEROMP@fda.hhs.gov).

Given that human subject safety is the traditional top concern of IRBs, it is no wonder that the initial portion of the guidance includes the following.

"FDA is aware that not all trials can be initiated or continued during disasters and PHEs, and for some trials, there may be no alternative to stopping the trial earlier than planned in order to safeguard participants' and trial staff's safety.

The determination of whether to continue a trial should be based first and foremost on ensuring that participants will continue to be able to participate safely ....

FDA outlines the following general considerations to assist sponsors in ensuring the safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity ....

III. DISCUSSION

A. Considerations for Continuing Trials

• Ensuring the safety of trial participants is paramount. Sponsors should consider above all whether participants can safely continue in the trial, including necessary modifications and risk mitigation steps to ensure safety ....

Study decisions might include those regarding continuing trial recruitment, continuing use of the IP [Investigational Product] for participants already in the trial, and the need to change participant monitoring during the trial. In all cases, it is critical that trial participants, IRBs/independent ethics committees (IECs), and regulatory agencies are kept informed of changes to the design and conduct of the study as appropriate" (supra at pp. 1-2).

To Continue or Not To Continue

"• Sponsors should consider whether the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol, discontinuing the administration or use of the IP, modifying the assessments or assessment schedule, or discontinuing participation in the trial.

Such decisions will depend on specific circumstances, including the nature of the IP, the ability to conduct appropriate safety monitoring, the potential impact of the disaster or PHE on the IP supply chain, and the nature of the disease or condition under study in the trial.

Sponsors should work with the investigators conducting the trial to assess the individual participant's situation and risk profile when considering their status in the trial.

• Screening procedures (e.g., testing for an infectious disease) that may be mandated by the health care system in which a clinical trial is being conducted may not need to be included as an amendment to the protocol if the sponsor does not plan to incorporate the data collected as part of a new research objective" (ibid). © {TBC}

IRBs and Risk-Based Monitoring of Studies (#2)

IRBs and the monitoring of human subjects' studies go hand and hand. This is not new. However, what is new is a final FDA guidance on such monitoring.

Although not designed primarily for IRBs, the FDA recommendations can be useful for IRBs conducting their own monitoring, especially for situations where investigators also serve as the study's sponsor.

When sponsor-investigators are involved, of course, IRBs have the advantage of ready access to the investigators involved.

In addition, IRBs may wish to ensure that such steps are in place for the external sponsors with whom they interact to monitor and enhance subject safety.

The guidance in question, which we first discussed in the September HRR (p. 5) is titled "A Risk-Based Approach to Monitoring of Clinical Investigations -- Questions and Answers."

We resume our presentation of the guidance's highlights with FDA's note that subject safety monitoring has multiple benefits.

> "This system to manage the quality of the investigation should help ensure data integrity while safeguarding the rights, safety, and welfare of trial participants,[6] for example, by focusing on the design of efficient clinical trial protocols, tools for identifying and tracking potential risks, and procedures for data collection and processing" (guidance, April, p. 2; on the Web at https://www.fda.gov/media/121479/download).

Current Monitoring Regulations For IRBs Are Not Specific Enough

> "[FN #6: For FDA's regulatory definitions of *human subject* and *subject*, see 21 CFR 50.3(g), 56.102(e), 312(b) and 812.3(p).
>
> For the purposes of this guidance, the terms *human subject* and *participant* are used interchangeably.]
>
> This system should include a risk-based approach to monitoring tailored to the potential risks for the specific clinical investigation.
>
> Effective implementation of risk-based monitoring, including the prioritization of monitoring and other oversight activities directed at processes and procedures critical for human subject protection and maintaining data integrity, should help maximize the quality of a clinical investigation.
>
> Although FDA's regulations require sponsors to monitor the conduct and progress of their clinical investigations,[7,8] FDA regulations are not specific about how sponsors are to conduct monitoring.
>
> [FN #7: 21 CFR 312.50 requires a sponsor to, among other things, ensure 'proper monitoring of the investigation(s)' and 'that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND.'
>
> 21 CFR 812.4 states that sponsors are responsible for, among other things 'ensuring proper monitoring of the investigation,' and 21 CFR 812.46 requires, among other things, that sponsors take certain actions when they discover that an investigator is not complying with the signed agreement, the investigational plan, the requirements of 21 CFR part 812 or other applicable FDA regulations, or any conditions of approval imposed by the reviewing institutional review board or FDA.]
>
> [FN #8: See also CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.]" (ibid).

Protecting Human Subjects Remains a Top Priority

> "FDA recommends that sponsors use a risk-based approach to develop their monitoring plans and to revise their monitoring plans, if needed, as the clinical investigation proceeds.
>
> This risk-based approach should be informed by the sponsor's overarching quality management activities undertaken in the development of the protocol and associated investigational plans and should be adjusted throughout the conduct of the investigation as needed.
>
> As described in the 2013 RBM [Risk-Based Monitoring] guidance, FDA recommends that at the protocol design stage, sponsors identify the critical data and processes necessary for human subject protection and maintaining data integrity for the investigation.
>
> Once these are identified, sponsors should perform a risk assessment and determine whether risks to critical data and processes may be mitigated through revisions to the protocol and investigational plans.
>
> When risks cannot be resolved through such revisions, sponsors should determine how remaining critical risks will be identified, tracked, and managed via the sponsors' monitoring plan or related study oversight plans during the conduct of the investigation" (supra at pages 2-3).

© {TBC}

IRBs and Expanded Access Submissions (#2)

As we introduced last month (see October's HRR, p. 6), a final version of an FDA guidance contains numerous tips on the role that IRBs do or do not face regarding "expanded access" protocols.

We resume here where we left with off our presentation of guidance highlights by excerpting more from the "Background" section, as follows:

"For an investigational drug or biological product to be provided through the expanded access pathway, the sponsor of the investigational drug or biological product must agree to provide such access.

Although the drug requested under individual patient expanded access is investigational, use of that drug through individual patient expanded access is for the primary purpose of diagnosing, monitoring, or treating a patient's disease or condition, rather than generating scientific data intended to characterize the safety and effectiveness of a drug[7]" ("Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions for Investigational Drugs and Biological Products," September, p. 2; on the Web at https://www.fda.gov/media/171902/download).

Three Types of "Expanded Access" Submissions Are Relevant for IRBs

"[FN #7: See 21 CFR 312.300. See also the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers*.]

Under FDA regulations, there are three categories of expanded access submissions: individual (also known as single) patient, including for emergency use; intermediate-size for intermediate-size patient populations; and 'treatment' for larger populations.[8]

[FN #8: See 21 CR 312.310, 312.315, and 312.320.]

This guidance only applies to IRB review of individual patient expanded access submissions as outlined in 21 CFR 312.310.[9]

[FN #9: See 21 CFR 312.310.]

This guidance does not address IRB review of intermediate-size and 'treatment' expanded access submissions, as outlined in 21 CFR 312.315 and 312.320, respectively.

An individual patient expanded access request can be submitted to FDA by a licensed physician as a new investigational new drug application (IND) or by a sponsor of an existing IND as a protocol amendment, either on an emergency[10] or non-emergency use basis.[11]

[FN #10: FDA considers an emergency situation to be, for example, a situation that requires a patient to be treated before a written submission to the IRB can be made and in which the treatment is expected to have a rapid effect in resolving an acute clinical emergency.]

[FN #11: See 21 CFR 312.310.]

A request for emergency individual patient expanded access does not require prior IRB review, but the IRB must be notified within 5 working days of treatment initiation.

Generally, once an investigational drug is used in an emergency situation without prior IRB approval, any subsequent uses of the investigational drug at that same institution would require prior IRB review and approval.

An institution or physician that expects subsequent use of the investigational drug should request review and approval by the appropriate IRB after the initial emergency use" (supra at pp. 2-3).

IRBs Have Some Leeway In Conducting a Review

"However, when prior IRB review and approval is not feasible for a subsequent expanded access emergency use at a particular institution, FDA does not intend to deny the subsequent request for emergency use based on lack of time to obtain prospective IRB review, provided that use will be reported to the IRB within 5 working days of initiation of treatment.[12]

[FN #12: See the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers* and 21 CFR 56.104(c).]

For non-emergency expanded access requests for individual patients, prior IRB review and approval is required before treatment begins.[13]

[FN #13: See 21 CFR 312.305(c)(4) and 56.103.]

[Nevertheless,] A licensed physician who submits a non-emergency individual patient expanded access request may request from FDA a waiver[14] of the requirement for full IRB review.[15]

[FN #14: See 21 CFR 56.105.]

[FN #15: See 21 CFR 56.108(c).]."

IRBs and Reaction to Changes In Pediatric Research (#3)

We this article we conclude presenting highlights from SACHRP's response to recent FDA proposals to modify pediatric research regulations. These proposals will affect how IRBs review and approve/disapprove research with children. We resume where we left off with our previous article on this topic (see the August HRR, p. 4).

"Some may read the [FDA's] Draft Guidance and conclude that the FDA appears to [believe] that the use of a placebo is equivalent to withholding effective therapy. However, there are examples of clinical investigations where the use of a placebo is ethically more complex.

For example, there is a difference between the use of a placebo while withholding known effective treatment versus research where the placebo (or investigational drug) is used, in conjunction with a known effective treatment, as an add-on to assist in masking randomization to different treatment arms" ("SACHRP Recommendations on Draft Guidance *Ethical Considerations for Clinical Investigations of Medical Products Involving Children: Guidance for Industry, Sponsors, and IRBs*," April 4; on the Web at https://www.hhs. gov/ohrp/sachrp-committee/recommendations/sachrp-recommendations-on-draft-guidance-ethical-considerations-clinical-investigations-medical-products/index.html).

"Assent" of Children Is Crucial

"The ICH E10 (Choice of Control Group [in International Conference on Harmonisation reference work, No. E10]) includes several examples of study designs that may include a placebo.[10]

[FN #10: See https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf.]

Based on what the FDA has said in the Draft Guidance about 'placebo' and 'prospect of direct benefit,' it is not clear how the FDA would expect IRBs to apply Subpart D to various study designs that utilize placebo.

Given the significance of the use of placebos in an IRB's determinations regarding prospect of direct benefit, SACHRP recommends that FDA provide other examples of the use of a placebo in different study designs, and the resulting analysis, as reflected in ICH E10 Choice of Control Group.

Other examples of the use of component analysis would be helpful, whether in this or future guidance or other venues.

Parental/Guardian Permission and Child Assent

The regulations state that 'assent' means a child has provided affirmative agreement to participate in a clinical investigation; mere failure to object should not be construed as assent (21 CFR 50.3(n)).

Unless the IRB waives the requirement, adequate provisions must be made for soliciting assent from the children if the IRB determines that the children are capable of providing assent (21 CFR 50.55(a)), taking into account the ages, maturity, and psychological state of the children involved" (ibid).

Age Alone Is Insufficient Criterion

"This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate. (21 CFR 50.55(b))

SACHRP recommends that the Draft Guidance clarify that the reference to children 7 years of age and older often being considered capable of assent does not constitute an absolute threshold.

IRBs may determine that in some circumstances children younger than 7 are capable of assent, but in other circumstances the age at which obtaining assent is appropriate will be older than 7.

IRBs need to make determinations based on the circumstances of the proposed research and the population being studied, taking into consideration the ages, maturity, and psychological state of the children involved in the clinical investigation. (21 CFR 50.55(b))

SACHRP recommends that the Draft Guidance include commentary on issues that arise when there is discordance between the wishes of the parent/guardian and the child regarding participation, e.g., when a parent/guardian gives permission but [the] child does not give their assent or where a child wishes to participate in research but the parent/guardian refuses to give their permission.

The guidance should direct investigators to engage with the IRB when such scenarios are encountered. Although the regulations do not require assent when the research offers the prospect of direct benefit, there may be circumstances when the child's refusal to give assent should be respected even when parents give permission" (ibid). © {TBC}

Multi-Agency Review of Pediatric Research (#6)

We present here more IRB-focused elements from the FDA's recent guidance titled "Research Involving Children as Subjects and Not Otherwise Approvable by an IRB: Process for Referrals to FDA and OHRP."

We resume our coverage by picking up where we left off in the October HRR (p. 4) with FDA's recommendations for IRBs on what they should do, and not do, regarding such research.

"D. Recommendations

For PAC/PES [FDA's Pediatric Advisory Committee/Pediatric Ethics Subcommittee] meetings, after deliberations and discussion of the clinical investigation, the PAC/PES will vote on whether to recommend that the proposed clinical investigation may proceed under 21 CFR 50.51, 50.52, 50.53, or 50.54[7].

[FN #7: Although the PAC/PES meeting will focus on whether the clinical investigation is approvable under 21 CFR part 50 subpart D, the clinical investigation also must comply with all other applicable requirements, including but not limited to those in 21 CFR part 50, subparts A and B, and in 21 CFR part 56.]" (guidance, March, p. 10; on the Web at https://www.fda.gov/media/166731/download).

When Comments Will and Will Not Be Posted Publicly

"The [FDA's] PAC/PES members will not write individual recommendations regarding whether the research meets the criteria in 21 CFR 50.54(b)(1) or (2).

[In contrast,] For OHRP expert panel meetings, after deliberation and discussion of the proposed research, each panel member will write an individual recommendation discussing whether the research meets the criteria of 45 CFR 46.407(b)(1) or (2).

OHRP will post the individual panel member recommendations in the docket. To allow time for comments on the posted expert panel recommendations, the public may continue to provide comments in the docket for 30 days after the date of the expert panel meeting.

VI. Final Determination

FDA specific information:

After the PAC/PES meeting, FDA staff will develop and send a memorandum that outlines the PAC/PES recommendation(s) and that includes any FDA staff comments and recommendations, as well as relevant supporting documents, to the FDA Commissioner (or delegee).

The memorandum may include recommended changes to the research protocol and/or changes to the parental/guardian permission and assent forms that the PAC/PES and/or FDA staff believe are necessary for the clinical investigation to proceed under subpart D, as well as any suggested changes that might enhance the clinical investigation (e.g., strategies to ease study burden on patients and care providers, strategies to improve trial enrollment).

The memorandum will request the Commissioner (or delegee) [to] make a final determination as to whether, and if so, under which provisions of subpart D, the clinical investigation may proceed.

After the Commissioner (or delegee) has made a final determination, FDA intends to forward the determination to the IRB and post the final determination on the FDA website within 90 days of the PAC/PES meeting or as soon as practicable thereafter. FDA will post the PAC/PES transcripts and meeting documents on the FDA website when available" (supra at pp. 10-11).

Both Federal Agencies Will Provide Recommendations

"*OHRP specific information:*

After the OHRP expert panel meeting, OHRP will develop a recommendation for the Assistant Secretary for Health (ASH) based on panel deliberations, reports, public comments, and its own analysis.

The recommendation may include changes to the research protocol and/or changes to the parental/guardian permission and assent forms that an expert panelist or OHRP staff believe are necessary for the research to proceed under subpart D, as well as any suggested changes that might enhance the research (e.g., strategies to ease study burden on patients and care providers, strategies to improve trial enrollment).

OHRP then will submit its recommendation and relevant documents to the ASH [Assistant Secretary for Health, HHS]. After review of the relevant materials and OHRP's recommendations, the ASH, on behalf of the HHS Secretary, will make the final determination regarding whether the research may proceed under 45 CFR 46.404, 46.405, 46.406, or 46. 407" (ibid). © {TBC}

IRBs and Research With Children (#9)

We resume here with more tips for IRBs from a recent FDA guidance on research with children, as we continue on from our July article (p. 4) on benefit-risk issues. Weighing benefits and risks in such studies is often a challenge for IRBs.

"The necessary evidence to determine *prospect of direct benefit* for a pediatric clinical investigation may be based on one or more sources of information. When adult data are available in conditions that exist both in adults and children, evidence of a clinical benefit from the drug or device in adults can provide support for *prospect of direct benefit* before clinical investigations are initiated in children" ("Ethical Considerations for Clinical Investigations of Medical Products Involving Children," September, 2022, p. 6 of 14; on the Web at https://www.fda.gov/media/161740/download).

All Types of Data Are Relevant For Benefit-Risk Analysis

"Animal or relevant device modeling and simulation data may provide evidence of *prospect of direct benefit*; and, in conditions that exist in both pediatric and adult populations, may preclude or mitigate the need to preliminarily collect relevant adult data.

For pediatric conditions with a phenotype that extends into adulthood, demonstration of a drug's favorable effect on a biomarker(s) or surrogate endpoint(s) linked to the causal pathway of the disease in adults may also support *prospect of direct benefit* in children.

For conditions with manifestations that occur exclusively in children, collection of adult data evaluating the drug or device may not be available or feasible, and nonclinical data obtained in a relevant animal or in vitro model for the condition of interest may often be the only source of information to support *prospect of direct benefit* ....

21 CFR 50.52(a) requires that the IRBs find that the risk is justified by the anticipated benefit to subjects. Assessment of the risk is predicated on adequate safety data. All available clinical data -- such as data collected from healthy adults, if appropriate; adults with the same condition; or adults or children treated with the same drug or device for a different indication -- should be included in the risk analysis" (ibid). © {TBC}

IRBs and Pediatric Studies of Drugs (#5)

As we noted previously, there has been an unusual number of FDA guidances issued recently for IRBs and researchers on studies involving children.

In this HRR article, we continue from the August HRR (p. 4) by presenting more key excerpts from FDA's revised draft guidance titled "General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products."

We resume with more IRB tips on risks posed by the common blood and/or fluid sampling taken in research projects. Typically routine, such sampling still must represent no more than a "minor increase over minimal risk."

"The limited venipunctures to obtain specimens for PK [pharmacokinetics] analyses would generally be considered either minimal risk or a minor increase over minimal risk, and therefore could be approvable by the IRB even without the prospect of direct benefit (see 21 CFR 50.51(a) and 50.53(a))" (guidance, September, 2022, p. 9 of 25; on the Web at https://www.fda.gov/media/90358/download).

"Component Analysis of Risk"

"This approach to the analysis of clinical trials is often called a *component analysis of risk*, whereby to determine the overall acceptability of the clinical investigation, the risks and anticipated direct clinical benefits of the interventions included in a protocol are analyzed individually as well as collectively.[32,33,34]

[FN #32: See ... *Research Involving Children: Report and Recommendations of the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, (43 FR 2084, 2086), Jan. 13, 1978.]

[FN #33: See Preamble to the Final Rule, *Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products,* (78 FR 12937, 12937-12950), February 26, 2013.]

[FN #34: See the FDA guidance entitled *Acute Bacterial Otitis Media: Developing Drugs for Treatment* (October 2012).]

An example of a clinical pharmacology study that generally would fall under 21 CFR 50.53 is the pharmacokinetics of the oral administration of a *single dose* of an over-the-counter cough and cold product" (ibid). © {TBC}

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

HUMAN RESEARCH REPORT™

OHRP Investigation of IRBs and Researchers

Project Title: Human Research Protections Under Federalwide Assurance No. 4952 (New York University Grossman School of Medicine) (*Part #8*)

Investigating Agency: Office for Human Research Protections (OHRP) of the Department of Health and Human Services (HHS)

Allegations: "Not-for-cause" investigation of overall human subjects protection system becoming "for cause" following concerns of the National Institute of Mental Health (NIMH)

Reference: OHRP letter of March 21, 2022, to Imad Alsayed, M.D., Vice President, Clinical Research Operations and Regulatory Affairs; from Lisa Buchanan, MAOM, CIP, OHRP's Director of Compliance Oversight

* * *

University's Internal Investigation Found Several IRB Problems

With this article we conclude our presentation of highlights from this federal investigation of IRB operations and related events at New York University.

We resume where we left off with the University's explanation to OHRP of what it had done to correct past noncompliance findings and prevent future ones.

"As a result of the RRS [the University's Research Regulatory Services office] audit the following has made the following findings and determinations responsive to the specific areas identified in OHRP's July 13, 2020[,] letter [sic]:

'• RRS rarely identified problems with timely reporting of unanticipated problems (UAPs) and timely reporting of non-compliance.

• RRS identified a small number of issues involving changes in protocols without IRB approval; examples include cases where: NYU employees were enrolled without IRB approval, the number of enrolled subjects exceeded the number approved by the IRB, there was failure to obtain prospective IRB approval of enrollment deviations, and there was performance of assessments not specifically identified in the approved protocol.

• RRS identified a small number of issues with PIs' failure to obtain documentation of informed consent as required by the Common Rule; examples include use of incorrect consent form versions, missing dates or signatures of study team, lost/misplaced consent forms, and infrequent cases of optional procedures conducted on subjects who had not opted-in to the research procedures.

• RRS identified a small number of issues involving failure of PIs to follow protocol requirements, including audit findings around PI non-adherence to inclusion/exclusion criteria, [;] incomplete, unsigned, or delayed signature of eligibility checklists; unreported protocol deviations; discrepancies between source, case report forms, and other study documentation; enrollment of subjects with unmet or undocumented eligibility criteria; and failure to conduct all protocol-mandated tests/procedures and/or study visits.' "

Paramount Role of Subject Safety

"Additionally, NYU stated:

'When any non-compliance impacting subject safety is discovered, this must be reported to the IRB Director and IRB Chair as immediately as possible, but, in all cases, within no more than one (1) business day of discovery of the issue.

When any non-compliance with the potential of impacting subject safety is discovered, this must be reported to the IRB Director and IRB Chair within no more than one (1) business day of investigation conclusion (and such investigation must commence within no more than two (2) business days of discovery).' "

OHRP Is Satisfied With University's Corrective Actions

" 'Further, any audit with major findings of non-compliance and/or any for-cause audit must be reported to the IRB Director within no more than one (1) week of audit conclusion.

Any routine audits with major findings of non-compliance must be reported to the IRB Director within no more than three (3) weeks of the audit conclusion ....'

OHRP has concluded that the corrective actions implemented by NYU described in this letter adequately address the concerns identified during the 2015 OHRP site visit.

At this time, there should be no need for further involvement by our office in this matter. We appreciate your institution's continued commitment to the protection of human research subjects." ©

FDA Warning

Warning Letter to: Jack Carlton F. Hazelwood, Ph.D., IRB Chairman, Burzynski Research Institute (BRI), Houston, TX (#1)
Investigation Period: January 22, 2013, to February 7, 2013
Warning Letter Date: September 23, 2013
Noncompliance: IRB failure to follow four sets of federal regulations on protecting human subjects (including repeats of past noncompliance events); restrictions imposed by FDA; and eventual closure of IRB

* * *

IRB's Explanations Are "Unacceptable"

"Dear Dr. Hazelwood:

This letter imposing restrictions (IRB Restrictions Letter) informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of the BRI Institutional Review Board (BRI IRB) that was conducted between January 22, 2013, and February 7, 2013.

The purpose of this inspection was to determine whether the IRB's activities and procedures for the protection of human subjects comply with FDA regulations published in Title 21 of the CODE OF FEDERAL REGULATIONS (21 CFR), parts 50 and 56.

These regulations govern clinical investigations of products regulated by FDA, and help ensure that human subjects are protected from undue hazard or risk during the course of clinical investigations. At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was presented and discussed with you.

We acknowledge receipt of the IRB's February 28, 2013, written response to the Form FDA 483, and a follow-up response dated March 28, 2013. We have reviewed the FDA inspection report, the Form FDA 483, and your responses.

The IRB's written responses are unacceptable, as explained below. This IRB Restrictions Letter provides you with written notice describing BRI IRB's noncompliance with (violations of) applicable federal regulations governing the operation and responsibilities of IRBs under 21 CFR part 56.

The BRI IRB is required to respond in writing to FDA's Center for Drug Evaluation and Research (CDER), Office of Scientific Investigations (OSI), with a description of the corrective actions that will be taken by the IRB, the institution, or both, to achieve compliance with FDA regulations (21 CFR 56.120(a)).

The name and address of the person to whom you should submit your corrective action plan is provided at the end of the letter. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation ...."

"Expedited Review" for Cancer Treatment

"1. The IRB failed to follow FDA regulations regarding expedited review procedures (21 CFR 56.110(b)).

Under an expedited review procedure, the IRB's review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB.

Further, the IRB may use the expedited review procedure to review either or both of the following: (1) some or all of the research appearing on the FEDERAL REGISTER list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk; or (2) minor changes in previously approved research during the period for which approval is authorized."

IRB Misuses "Expedited Review" Procedure

"Our inspection revealed that the BRI IRB used expedited review inappropriately to approve Single Patient Protocols (SPPs) for patients who failed to meet enrollment criteria for open clinical investigations to receive antineoplaston therapy.

Based on our review of records from the inspection, as well as statements made by Mr. Gary L. Harvey, IRB Vice-Chairman, during the inspection, the IRB would grant 'provisional approval' before placing an SPP on the agenda for the next scheduled IRB meeting, and that upon granting this 'provisional approval,' the subject was able to receive treatment with antineoplastons.

A 'provisional approval' is not recognized by FDA as a valid IRB action. The IRB regulations provide for studies to be approved by either full board review or by expedited review when applicable. Because BRI IRB authorized the investigator to provide the investigational product to subjects after receiving 'provisional approval' and prior to a full board review, it appears that BRI IRB uses the term 'provisional approval' to mean approval via expedited review." © {TBC}

This newsletter is copyright protected and sold with a limited license. See p. 12 for details.

IRB Compliance Comment Deadlines & Notices

• **Department of Health and Human Services.** Comments are ***due by December 5*** on ***the numerous*** proposed changes to current regulations contained in the "PHS Policies on Research Misconduct."

These changes fill 21 pages of the usual 3-columned text in the FEDERAL REGISTER (pp. 69583-69604).

> "The proposed revisions are based on the experience ORI [Office of Research Integrity] and institutions have gained with the regulation ***since it was released in 2005***" (October 6, p. 69583).

For more information, contact: ORI's Sheila Garrity, JD, MPH, MBA, at 240-453-8200.

• **Food and Drug Administration.** Comments are ***due by November 20*** on the agency's request for public input on the:

> "... critical scientific challenges and opportunities to advance the development of individualized cellular and gene therapies (CGTs). FDA intends to gather information and comments submitted in response to this request for information (RFI) to inform potential planning ... of ***additional regulatory science tools, standards, or guidance***" (88 Fed. Reg. 65174-65175, September 21).

For more information, contact: Karen Fikes of FDA's CBER at 240-402-7911.

• **Food and Drug Administration.** Comments are ***due by November 26*** on a new draft guidance titled "Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment."

> "The purpose of this guidance is to assist sponsors in the clinical development of drugs, biological products, and certain devices for the prevention or treatment of acute graft-versus-host disease (aGVHD) or chronic graft-vs-host disease (cGVHD) ....
>
> This guidance focuses on ***clinical trial design***, statistical analysis, or other issues specific to aGVHD or cGVHD, and it does ***not*** contain a discussion of the general principles regarding statistical analysis, clinical trial design, or drug development" (88 Fed. Reg. 67302, September 29).

There are numerous references throughout the 36-page draft guidance to different types of ***benefit-risk factors for human subjects***.

The guidance itself is available on the Web at https://www.fda.gov/media/172524/download. For more information, contact: Robert Le of FDA's CDER at 240-402-8320.

• **Food and Drug Administration.** Comments are ***due by November 27*** on the agency's request for comments on its request to the Office of Management and Budget to ***extend its current approval*** for requirements regarding "Adverse Events" (AEs).

Specifically, FDA seeks input on OMB Control No. 0910-0308-Extension ("Adverse Experience Reporting For Licensed Biological Products").

> "The collections of information are intended to enable ***FDA to take actions necessary for the protection of the public health in response to reports of adverse experiences*** related to biologics licensed under any provision of section 351 of the PHS Act" (88 Fed. Reg. 66857, September 28).

FDA estimates that entities affected by the relevant regulations at 21 CFR part 600 and elsewhere ***annually consume over 11 million hours of record keeping and reporting. The overwhelming majority of this time is spent on making and submitting "Periodic Adverse Experience Reports."***

For more information, contact: Domini Bean of FDA's Office of Operations at 301-796-5733, or send email to PRAStaff@fda.hhs.gov.

• **Food and Drug Administration.** Comments are ***due by December 4*** on the agency's request for comments on a new draft guidance titled "Stimulant Use Disorders: Developing Drugs for Treatment."

In addition to ***containing recommendations useful to IRBs in their protocol reviews***, this guidance will:

> "... assist sponsors [and sponsor-investigators] in the clinical development of drugs for the treatment of stimulant use disorders .... [especially because] ***FDA has yet to approve any medication treatments for stimulant use disorders ....***" (88 Fed. Reg. 69205, October 5).

The guidance itself is on the Web at https://www.fda.gov/media/172703/download. For more information, contact: Matthew Sullivan of FDA's CDER at 301-796-1245.

• **Food and Drug Administration.** Comments are ***due by December 18*** on the agency's request for comments on a new draft guidance titled "Demonstrating Substantial Evidence of Effectiveness ***Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence***" (see https://www.fda.gov/media/172166/download).

The relevant September 19 FEDERAL REGISTER announcement is on page 64445. The FDA contact for more information is: CDER's Eithu Lwin at 301-796-0728. ©

IRB Compliance Conferences & Courses

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

• **November 14-15, 2023,** in Savannah, Georgia: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP Virtual Conference."** The topics will include: what to do during an FDA site inspection; current trends in the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials of drugs, devices, and biological products; key differences between experiments with drugs vs. devices vs. biologics; primary roles of FDA Centers; emerging issues in the ethics of human subject experiments; data quality control in clinical trials; responsibilities of PIs in FDA-regulated research; IRB regulations affected by recent changes to the Common Rule; changes in informed consent requirements; benefits and challenges in decentralized trials; and guidelines on the use of electronic data capture system. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or fax to 215-822-8633, or send an email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **December 3-6, 2023,** in Washington, D.C.: **"SBER Conference and 2023 PRIM&R's Annual Conference (PRIMR23)."** Meetings to be held at the Walter E. Washington Convention Center. Topics include: challenges for IRBs that oversee Decentralized Clinical Trials (DCTs); mastering FDA regulations; legal considerations in emerging SBER issues; public access to private research information; key HRPP/IRB administration topics; research in schools; human research in the digital world; AI and research ethics; studies with children outside of the classroom; subject populations requiring extra protections; new challenges to informed consent; institutional risks when IRBs choose to be the single IRB for multisite studies; biospecimen research; IRBs and communication with community members; and many other IRB-related areas. Contact: PRIM&R, Suite 720, 20 Park Plaza, Boston, MA 02216 at 617-423-4112, or send email to info@primr.org, or see their Web site at www.primr.org.

• **February 22-23, 2024,** in San Diego, California: **"Pediatric Clinical Trials Conference."** This conference will be presented by the Society of Clinical Research Associates (SoCRA). Topics will include: regulatory considerations in pediatric research; challenges in pediatric research; monitoring, auditing, and compliance; and recruitment, enrollment, and retention of human subjects in pediatric studies. Contact: Conference Registrar, SoCRA, 530 West Butler Avenue, Chalfont, PA 18914 at 800-762-7292, or send an email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **May 2-3, 2024,** in Nashville, Tennessee: **"17th Annual Device Research & Regulatory Conference."** The topics include: using human factors engineering to reduce medical errors; physiological research; and the role of IRBs in reviewing device research. Contact: SoCRA at 800-762-7292. ©

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

Kathleen Maloney, M.Ed., is the Associate Editor of the Human Research Report. Her degree is in Computers in Education and she is a former Honors English teacher. She has published nationally, won competitive grant awards, and received a special award from the Alice B. Buffet Foundation (a Warren Buffet Foundation). Also a mixed media artist, a selection of some of her works is available on the Web at KathleenMaloney.net.

MEMBER Since 1993 BBB BBB Rated as A+ ("Excellent")

Newsletter National Winner APEX'96 AWARDS FOR PUBLICATION EXCELLENCE

The **First Subscriber** listed below has paid for, and is licensed to, forward/print/photocopy/distribute the total number of copies of this newsletter that appears in the *red circle below*. Any additional forwarding/printing/photocopying/distributing of this newsletter is a violation of U.S. Copyright Laws, and it is actionable cause for the publisher to **take legal action** against any person(s) who so distributes *more than the number of copies listed in the red circle below.*

"X" number of licensed copies

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

2023 Subscription Prices*

$167 per year for 12 monthly emailed copies for the **First Subscriber**

Only $17 per year for 12 monthly emailed copies for **each Extra Subscriber**

(Extra copies are distributed by the **First Subscriber**)

(*Subscriptions are not available to libraries)

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

* * * * *

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