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Human Research Report™

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

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IRBs and Human Subject Eligibility In Clinical Cancer Trials (#1)

A new series of recommendations for IRBs and others involved in clinical cancer trials was issued by FDA in late April. The series consists of three separate new guidances, each of which is subtitled "Draft Guidance for Industry, Institutional Review Boards, and Clinical Investigators."

The three main titles are "Cancer Clinical Trial Eligibility Criteria: Washout Periods and Concomitant Medications," "Cancer Clinical Trial Eligibility Criteria: Performance Status," and "Cancer Clinical Trial Eligibility Criteria: Laboratory Values."

Although none of these new guidances exceed five pages in length, they contain considerable detail and most certainly warrant the attention of any IRB that reviews and/or monitors clinical cancer trials.

FDA is accepting comments from the public on the content of these guidances. FDA's contact information is listed at the end of this article.

"Washouts" and "Concomitant Medications"

The first guidance for which we present highlights is the one titled "Washout Periods and Concomitant Medications." We begin with a note that much of this guidance actually applies to all three documents.

> "The purposes of eligibility criteria are to select the intended patient population and reduce potential risks to trial participants. However, eligibility criteria are sometimes more restrictive than necessary, and expanding eligibility criteria to be more inclusive is one trial design consideration that may improve the diversity of clinical trial populations.
>
> This draft guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of investigational drugs regulated by CDER and CBER for the treatment of cancer.
>
> Specifically, this draft guidance includes recommendations regarding the appropriate use of washout periods and concomitant medical exclusions and is intended to assist interested parties, including sponsors and IRBs, who are responsible for the development and oversight of clinical trials" (89 Fed. Reg. 32440-32441 at p. 32441).

As noted previously, this first guidance contains information applicable to all three guidances, but we shall present such general advice this one time only, beginning with:

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}**.

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"A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population" (guidance, April, p. 1; on the Web at https://www.fda.gov/media/178016/download).

Subject Safety and Research Recruitment

"Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial.

The agency recognizes that some eligibility criteria may have become commonly accepted over time or used as a template across trials, but such criteria should be carefully considered and be appropriate for a specific trial context.

Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug[6,7] (p. 2).

[FN #6: Kim ES, Uldrick TS, Schenkel C, et al[.], 2021, 'Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO - Friends of Cancer Research Joint Research Statement,' Clin Cancer Res, 27(9): 2394-2399.]

[FN #7: Spira AI, Stewart MD, Jones S, et al., 2021, 'Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO - Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group,' Clin Cancer Res, 27(9): 2416-2423.]" (ibid).

Presence of "Comorbidities" in Cancer Patients

"A washout period is a treatment-free period between the most recent anti-cancer treatment and treatment with the investigational drug. This treatment-free period is intended to allow a prior therapy and/or its effects on the body to be eliminated or reduced to acceptable levels preventing additional toxicity when a new therapy is started ....

Concomitant medications are any prescription or non-prescription medications (i.e., over-the-counter drugs and dietary supplements) a patient may be taking in addition to the investigational drug product(s). Patients receiving anticancer therapies often have comorbidities that require drug therapy or cancer-related issues that require supportive care ...." (supra at p. 3).

Minimizing the Extent of Washout Periods

Section III of the guidance ("Recommendations") presents advice to IRBs such as:

"Eligibility criteria should be tailored to the investigational treatment, patient population being studied, and the goals of the clinical investigation. For that reason, the recommendations in this guidance reflect a general approach to broadening eligibility criteria related to washout periods and concomitant medications, rather than providing specific or prescriptive criteria.

Exclusion criteria should be justified with a disease- and drug-specific scientific rationale as opposed to vague statements such as, 'Exclude patients taking a concomitant medication expected to increase the risk for a clinically significant adverse event.'

Information about the pharmacokinetics/pharmacodynamics (PK/PD) of the expected previous treatments could inform the appropriate duration of the washout period. In addition, accumulated pharmacologic information for the investigational agent should be incorporated as soon as possible in subsequent clinical trials to minimize unnecessary washout periods and liberalize concomitant medication allowances.

Conducting drug-drug interaction evaluations early in drug development may inform selective dosing of the investigational or co-administered drug to a patient in subsequent trials and may facilitate enrollment of more patients in mid- to late-stage clinical trials" (supra at pp. 3-4).

FDA is accepting public comments on this and the other two guidances until June 25. For more information about this guidance on washouts and concomitant medications, contact: Jamie Brewer of FDA's CDER at 240-402-4463.

We will present highlights from the other two guidances in future HRRs and time and new IRB developments permit. © **{TBC}**

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IRBs To Be Evaluated On Effectiveness (#6)

We continue this month with more details on how IRBs, IRB members, and their institutions will be evaluated by federal agencies, probably in the not-too-distant future. In our opinion, now would be the best time to prepare for such evaluations, using guidances like the one we're presenting here for relevant information on how to face such assessments.

We resume where we left off in our presentation last month (p. 3) on the document titled "SACHRP Recommendation on GAO-23-104721, INSTITUTIONAL REVIEW BOARDS: Actions Needed to Improve Federal Oversight and Examine Effectiveness."

Of the various evaluation criteria areas listed by the SACHRP, we continue with the committee's recommendation on how to assess IRB compliance with the Belmont Principles. Of the four assessment areas for this particular compliance criterion, we resume with "Measurability."

Existing Agency Methods for Evaluating IRBs

"There are measures that have been developed for this [measurability] purpose. For example, researchers have provided suggestions for using equity impact assessment tools to measure beneficence and justice.[5]

[FN #5: Ruqaiijah Yearby, 'Exploitation in Medical Research: The Enduring Legacy of the Tuskegee Syphilis Study,' 67 Case W. Res. Univ. L. Rev. 1171 -1226 (2017);

Ruqaiijah Yearby, 'Missing the 'Target': Preventing the Unjust Inclusion of Vulnerable Children for Medical Research Studies,' 42 Am. J. of L. & Med 797-833 (2016);

Ruqaiijah Yearby, 'Involuntary Consent: Conditioning Access to Health Care on Participation in Clinical Trials,' 44 J. of L. Med. & Ethics 445-461 (2016).]

These tools can not only be used by IRBs to assess protocols, but also by the government to assess the effectiveness of IRBs. In addition, SACHRP has previously issued a recommendation on applying the principle of justice.[6]

[FN #6: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-consideration-of-the-principle-of-justice-45-cfr-46.html.]

Assessment of whether more administrative/procedural [steps are involved] *or more substantive ethics.*

This standard of effectiveness is more substantive than procedural.

Example of Effectiveness Measures

FDA, OHRP, and other agencies' findings regarding the appropriate application of the Belmont Principles as codified in Section 111 of the Common Rule can be documented in an FDA Form 483 and in OHRP determination letters.

• ***IRB Member and Staff Education***

IRB members and staff should have appropriate education on and knowledge of the regulatory and ethical requirements for the conduct of ethical research ....

As the charge to IRBs is to review each protocol individually, and there is great complexity and variability in the research reviewed by IRBs, this approach focuses on ensuring [that] the proper structure is in place as opposed to measuring the outcome" (SACHRP Recommendations ..., October 19, 2023; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-october-19-2023-letter/index.html).

Proving That IRB Members Are Qualified

"However, IRB member and staff education is a surrogate endpoint, not a true measure of outcomes and effectiveness. Furthermore, it is a very narrow measure given the many issues that could be included in a standard for IRB effectiveness.

Furthermore, well-trained IRB members or staff, despite their training, could be overburdened or face other issues which negatively impact IRB effectiveness.

Feasibility for Government to enact

Some Federal Agencies currently require IRB member and staff training and even testing. Agencies could recommend or require that IRB members or staff obtain certification or document training.

Measurability

Educational activities can be measured, just like standard education programs.

Assessment of whether more administrative/procedural or more substantive ethics.

This standard is more administrative, as it doesn't measure effect of the training on the ethics/regulatory compliance of the research.

Examples of Effectiveness Measures

1. Passing a test such as the CIP, CIM, or CCRP
2. Number of Staff with CIP, CIM, or CCRP Certification or an equivalent certification
3. Documentation of completed electronic training modules" (ibid). © **{TBC}**

IRBs and FAQs on Reviewing Research (#6)

We continue here with more IRB tips from the FDA guidance titled "Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors" (on the Web at https://www.fda.gov/media/88915/download).

We are focusing on the guidance's Q&A section that is largely comprised of new recommendations from FDA. These recommendations were produced by the agency in response to questions from IRBs around the country.

We resume now with where we left off last month with more IRB considerations when non-English speaking subjects are enrolled in a study.

This excerpt is from Step #2 of three steps described in Q&A #5 from IRBs around the country on actual studies involving non-English speaking subjects.

"The investigator, with the assistance of an interpreter if needed, answers any questions from the prospective subject.

There must be a witness to the oral presentation who must not be the person obtaining informed consent (21 CFR 50.27(b)(2))" (guidance, August, 2023, page 49).

Informed Consent Witness Should Not Be Related to Subject

"Furthermore, FDA strongly recommends [that] the witness be fluent in the language of the oral presentation.

The witness must, at a minimum, have sufficient proficiency in the language of the oral presentation to be able to attest to the information that was to the presented orally to the prospective participant (21 CFR 50.27(b)(2)).

In addition, if possible, the witness should not be related to the subject.

(2) At the time informed consent is sought, the subject is given the IRB-approved translated short form and a copy of the IRB-approved English version of the long form, which serves as the written summary.

(3) The short form is signed and dated by the subject or LAR.

(4) The witness signs both the short form and the copy of the IRB-approved English version of the long form. (Note that when an interpreter assists the person obtaining consent, the interpreter may serve as the witness, but is not required to do so.)

(5) The person actually obtaining consent signs the copy of the IRB-approved English version of the long form.

Step 3 -- Take Additional Actions Following Subject Enrollment

After the subject has been enrolled in the research, the investigator takes the following additional actions:

(1) If a subject was enrolled in the research using an untranslated long form to serve as the written summary, and if the investigator did not consult with the IRB chairperson (or designee) prior to enrollment of the subject who does not understand English, the investigator should promptly notify the IRB chairperson (or designee) that such a subject was enrolled.

(2) The investigator must obtain a translated copy of the IRB-approved English version of the long form that served as the written summary, which should be done promptly.

The investigator promptly submits it to the IRB for review and approval" (supra at pp. 49-50).

Interpreter Should Be Available Throughout Entire Study

"Once the translated long form/written summary is approved by the IRB, the investigator must provide it to the subject or LAR and should do so as soon as possible.

FDA considers this step essential to the requirement that informed consent be documented by the use of a written consent document and that the subject be provided a copy (21 CFR 50.27).

Many of the clinical investigations regulated by FDA involve ongoing interventions and may involve long-term follow-up.

For this reason, translation of the long form is critically important as a means of providing subjects or their LAR an ongoing source of information understandable to them.

Additionally, as noted above in Frequently Asked Question #3, FDA recommends that whenever subjects who do not understand English are involved in research, appropriate interpreter services be made available throughout the course of the research.

6. What should be considered when enrolling subjects with low literacy and numeracy?

Although a competent person who does not read and write well can give informed consent and enroll in a clinical investigation, the sponsor, clinical investigator, and IRB should consider whether any modifications to the informed consent process are necessary to ensure that the informed consent process is understandable" (ibid). © {TBC}

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IRBs and New Changes For Informed Consent (#4)

We resume here where we left off in last month's HRR article (May, p. 5) regarding FDA's recent guidance titled "Key Information and Facilitating Understanding in Informed Consent: Guidance for Sponsors, Investigators, and Institutional Review Boards" (see https://www.fda.gov/media/176663/download).

We begin with an interesting, and not always considered, feature of informed consent that finishes FDA's presentation of its second topic ("*2. Purpose of the Research, Expected Duration, and Procedures To Be Followed*") on "key information."

> "Interested parties should also consider providing information on how an investigational medical product and/or participation in the study is similar to or different from the care [that] the prospective subject would receive if not enrolled in the study" (p. 7).

Presenting Most Common and Serious Risks First

> "*3. Reasonably Foreseeable Risks and Discomforts*[20]
>
> [FN #20: 21 CFR 50.25(a)(2) and 45 CFR 46.116(b)(2).]
>
> The discussion of risks and discomforts is generally among one of the most important and complex required elements of informed consent, and we recommend that this topic be addressed in the key information section.
>
> We recommend providing information about the most common and serious risks and discomforts in the key information section to inform a prospective subject's decision about participation.[21]
>
> [FN #21: See, e.g., the 'Informed Consent Discussion Tool' in Lentz, J, M Kennett, J Perlmutter, and A Forrest, 2016, 'Paving the Way to a More Effective Informed Consent Process: Recommendations from the Clinical Trials Transformation Initiative,' Contemp Clin Trials, 49:65-69, p. 67, doi: 10.1016/j.cct.2016.06.005.]
>
> Key information about risks and discomforts of research participation should be included on the first page of the key information section, if possible. If the key information section does not include all risk-related information, the key information section should note that fact and include a page cross-reference (or hyperlink for electronic documents) that directs prospective subjects to the appropriate section of the consent form where complete information is located.
>
> To help prospective subjects [to] assess risks, interested parties should consider prioritizing key risks from any investigational medical products, research procedures, or other aspects of the study, at the beginning of the information about risks.
>
> It may be appropriate in the key information section to present only the most important risks or discomforts based on frequency or magnitude, rather than listing all reasonably foreseeable risks.[22]
>
> [FN #22: See Office for Human Research Protections, 'Attachment C -- New 'Key Information' Informed Consent Requirements: SACHRP Commentary on the New 'Key Information' Informed Consent Requirements,' October 17, 2018; available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachmenet-c-november-13-2018/index.html. The recommendations in this draft guidance concerning reasonably foreseeable risks in key information are consistent with SACHRP's recommended approaches.]" (supra at pp. 7-8).

Study Could Worsen Patient's Condition

> "In clinical studies involving investigational medical products, the possibility that the product may present unknown risks to prospective subjects should generally be included as key information. Information about any potential risks should be explained in detail when possible, including, as applicable, the possibility that participation may not improve or could exacerbate a prospective subject's condition.
>
> We recommend that interested parties clearly delineate between risks and discomforts associated with a investigational medical product or other investigational procedures (e.g., educational or behavioral health interventions) and the risks and discomforts associated with other research interventions or procedures (e.g., additional imaging studies that would not ordinarily be part of clinical care).
>
> Also, the degree to which the risks and potential benefits in the study are likely to differ from the risks and benefits of clinical care should be included as key information when appropriate.
>
> In some cases, the key information section may include actions that will be taken to monitor and mitigate risks, such as planned safety monitoring, dose adjustments, or discontinuation of a subject's participation in research" (supra at page 8). © {TBC}

IRBs and "Best Interests" Standard For Human Research Subjects (#2)

We continue here with more key highlights from a new set of recommendations on IRB operations that was issued by the influential Secretary's Committee on Human Research Protections (SACHRP).

Titled "SACHRP Recommendation on Interpretation of the Best Interests Standard for the Retention of Subjects in Human Subjects Research that Has Been Suspended or Terminated," the document contains numerous tips for IRBs.

SACHRP's recommendations focus on various scenarios when, for one reason or another, a clinical trial must cease before it is concluded. We resume with SACHRP's point that:

> "Subjects who are in research studies that are being suspended or terminated may believe that they are receiving benefit from their participation, even when the subjects have been randomized to placebo or where clinical data from the research indicates that the intervention is ineffective or perhaps harmful" (SACHRP Recommendation ..., March 20, in "Defining 'Best Interests' " section).

Stopping a Study May Be "Inevitable" for Various Reasons

"It is inevitable that there will be clinical trials that are stopped due to negative overall results (either at the planned interim analysis or at the final analysis) even though there may be perceived benefit by persons who want to continue receiving the intervention.

In the context of individuals who lack capacity to make decisions in the clinical care context, an objective best interests test guides decision-making for people who never had capacity to make decisions for themselves, including children.

Legally, it is generally a consideration of whether the benefits outweigh the burdens.

In the context of research, it may be necessary to distinguish between a 'best interests' standard *i.e.*, benefits outweigh burdens in situations in which someone has a compelling interest in maintaining access to interventions or procedures that are only available through participation in research.

The other context in which best interests is used in cases relating to medicine is when a provider has put his/her/their own interests above the interests of the patient.

This expresses a concern about the fiduciary duty that physicians and other clinicians owe to patients.

Whether the duties owed by researchers to research subjects should be considered fiduciary is debated in the literature.

In the conduct of research, the research requirements for extra tests and procedures are not necessarily advancing the best interests of the patient-subject.

This is permissible in the research context because of the informed consent of the subject to participate in research. However, investigators still must provide for subject safety, but they are not expected to put the patient-subject's interests above all else.

Analysis of 'Best Interests'

Stakeholders in the research enterprise who have a part in deciding if subjects' continued participation is warranted in research that has been suspended or terminated must consider whether it is in the subjects' best interests to resume participation in some or all research procedures" (supra in "Analysis of ..." section).

Multiple Factors Must Be Considered on Subject Safety

"This analysis should be rooted in the principles of beneficence and non-maleficence and [in] the requirements that efforts are made to secure the well-being of subjects and not unnecessarily expose them to harm.

Factors that should be considered when making a best interests determination include:

- The reason for the suspension or termination.
- Whether subjects will continue to receive direct benefit (e.g., clinical benefit) if allowed to continue.
- The impact of the suspension or termination on the health and wellbeing of subjects.
- Whether the benefit requires the resumption of some or all research procedures.
- The risks to the subject associated with the resumption of some or all research procedures.
- The availability of resources to safely resume some or all research procedures.
- The ability to obtain the same care or treatment outside of the research context. [and]
- The need for the continued collection of safety data or for subject monitoring" (ibid).

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IRB Waivers for Minimal Risk Investigations (#3)

We resume this month with additional coverage of newly proposed IRB regulations on informed consent that we partially presented last month in the May HRR (see p. 4). We are focusing on the negative comments received by FDA when it published the earlier proposed version of its changes to existing IRB regulations at 21 CFR Parts 50, 312, and 812. The changes affect IRB reviews of "minimal risk" research.

Our focus on the objections can assist those IRBs and researchers who may face resistance or even outright opposition from reluctant prospective subjects.

We continue now with more of FDA's "Response" to "Comment 3" in which objectors opined that FDA's proposed informed consent changes violated the U.S. constitution. FDA states that:

"One comment cites a Federal district court case, *Merriken v. Cressman*, 364 F.Supp. 913 (E.D. Pa. 1973), for the general proposition that Federal courts have applied a requirement for fully voluntary informed consent grounded in constitutional law to social, behavioral, and biomedical research.

Contrary to the comment's assertion, however, the court did not decide in *Merriken* whether informed consent is required for participation in all research as a general matter" (88 Fed. Reg. 88228-88249 at p. 88232, December 21, 2023).

Court Case Does Not Impose Restriction on IRBs

"The case involved a program designed to help a school district identify potential drug abusers. *Id.* at 914. The court found that part of this program represented an invasion of an individual constitutional right to privacy that was not outweighed by the government's public need for information. *Id.* 918, 921.

The court then went on to address the standard for and adequacy of consent to waive a constitutional right to privacy involving an invasion of the parent-child relationship, rather than consent to participate in FDA-regulated minimal risk research. [Thus,] *Merriken* does not prevent FDA from finalizing this rule.

Of those comments that identify particular constitutional Amendments or rights, none provides [sic] specific facts or a legal basis for their claims that the rule would violate those provisions or rights. We are thus unable to provide a specific response to those comments.

However, we note that the rule does not require a[n] IRB to waive or alter informed consent, nor does it require any entity, including any government entity, to conduct or support any research.

Therefore, to the extent that conducting a particular clinical investigation with a waiver or alteration of informed consent could be viewed as interfering with a constitutional right, this rule does not require an IRB to grant such a waiver or alteration or require that the research be conducted.

In addition, we are clarifying, as requested by one comment, that constitutional rights are among the rights that may be appropriate for a[n] IRB to consider when determining if the criterion in §50.22(d) of the final rule (which requires the IRB to find that '(t)he waiver or alteration will not adversely affect the rights and welfare of the subjects') is satisfied" (ibid).

New Consent Requirements Apply Only To "Minimal Risk" Studies

"Finally, we note that some of the comments that question the constitutionality of the rule appear to be concerned about potential waivers of informed consent for research involving 'invasive procedures.'

It is important to emphasize that the provision for a waiver or alteration of informed consent being finalized in this rule is available only for clinical investigations that involve no more than minimal risk to the subjects and meet the other criteria in §50.22.

In general, we do not believe that a study involving an invasive procedure being used for research purposes would qualify as presenting no more than minimal risk to subjects.

(Comment 4) A few comments oppose the proposal because it would not restrict or prohibit waiver of consent for classified research, citing President Clinton's Memorandum of 1997 regarding classified research.

(Response 4) We do not believe it is necessary to address classified research in this rulemaking. As noted in some of these comments, the Clinton Memorandum is directed to Agencies that may conduct or support classified research subject to the 1991 Common Rule.

FDA's informed consent regulations apply to all clinical investigations, as defined in §50.3(c) (21 CFR 50.3(c)), involving FDA-regulated articles. FDA does not regulate research on the basis that it is federally conducted or supported" (supra at pp. 88232-88233). © **{TBC}**

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IRBs and Studies Using "Real World Evidence" (#2)

With this article we conclude our presentation of highlights from a new draft FDA guidance titled "Real World Evidence [RWE]: Considerations Regarding Non-Interventional Studies for Drug and Biological Products" (see https://www.fda.gov/media/171667/download).

The rising use of RWE by researchers, and the increasing acceptance of such studies by agencies such as the FDA, means that IRBs are likely to see more protocols submitted for review that involve RWE.

Hence, traditional IRB review topics such as human subject eligibility and the ethical adequacy of study design are likely to become even more important when RWE experiments are involved.

We resume our coverage with the guidance's recommendations on study design.

Major Elements in Study Designs for IRB Reviews

"Based on the prescribed research question(s) identified, the sponsor should develop study design elements. Each protocol should concisely describe each of the critical elements listed below:

- Schema to describe overall study design as well as a causal diagram to specify the theorized causal relationship
- Source population (i.e., the population from which the study population will be drawn)
- Eligibility criteria and the study population (i.e., the population for which analyses will be conducted)
- Conceptual and operational definitions for key variables of interest and the status of validation efforts for operational definitions, as relevant
- Relevant covariates (e.g., concomitant treatments) and corresponding strategies to address potential bias
- Index date (time zero) for all study arms and the approach to assigning an index date, including strategies to address potential bias introduced by issues related to *immortal time*[19]

[FN #19: In this guidance, *immortal time* is follow-up time in a study during which participants must 'survive' to be evaluated for an outcome event.]

- Start and end of follow-up (at-risk) period, planned approach to censoring, and anticipated losses to follow-up (including depletion of susceptible patients)

D. Data Sources

Sponsors should demonstrate the appropriateness of the proposed data source(s) to address specific hypotheses and research questions.

Given that data sources used in a non-interventional study design are often generated for purposes other than research, it is important that sponsors understand the potential limitations of such data sources and determine whether those limitations can be addressed or if another data source should be pursued.

Each protocol or accompanying documents should concisely describe each of the elements listed below ..." (guidance, March, pp. 5-6).

Data Accuracy Vital to Ensuring Ethical Research

"• Description of the proposed data source(s), including how the data were originally collected
- Rationale for choosing the data source(s)
- Relevance of the data to the drug-outcome association of interest
- Appropriateness of the information on relevant confounding factors
- Available information on data reliability (including method of accrual from source data)
- Description of common data models used to provide a standard structure for sharing data from various sources and the rationale behind the choice of the specific model
- Available information on the timing of assessments for key data elements and completeness of these key data elements
- Explanation of how the proposed coding is appropriate based on operational definitions of key variables
- Appropriateness of the data relative to the target patient population
- Quality assurance activities that will be performed on the extracted original source data
- Plans for additional data collection, as applicable" (supra at pp. 6-7).

There also is a final section of the guidance titled "E. Analytic Approach." That portion addresses various statistical measures that should be followed, primarily to ensure the accuracy of any analysis methods used or conclusions drawn about the study objectives and/or findings. ©

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OHRP Investigation of IRBs and Researchers

Project Title: Human Research Protections Under Federalwide Assurance No. 337 (Biomedical Research Alliance of New York - BRANY) (*Part #7*)
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
Reference: OHRP letter of July 13, 2022, to Raffaella Hart, MSHS, CIP, Senior Vice President for IRB and IBC Services; from OHRP's Amanda P. Sly, MS, CIP, Compliance Officer

* * *

How and When Was Consent "Waiver" Approved?

We resume our coverage of this investigation with more on OHRP's finding that the BRANY IRB did not adequately explain its use of a waiver in a study. This was OHRP's fifth area of possible noncompliance on BRANY's part that was assessed by OHRP.

"OHRP requested that BRANY clarify which portion(s) of the study these waivers apply and how this was documented in the review cycle.

OHRP also requested clarification regarding whether the key information was presented first during the oral consent, in accordance with the requirements of 45 CFR 46.116(a) and (a)(5)(i).

Response: According to your response [OHRP said], Phase 1 included focus groups with practitioners, focus groups with teens, and the pilot study. Phase 2 included the standard care/enhanced standard care activity. There were several phone calls and email conversations that occurred during the IRB review cycle with the researcher and the IRB staff, as well as between the IRB reviewer and IRB staff.

Each phase was carefully considered and the regulations regarding informed consent were carefully applied to each phase and subgroup.

The initial screening of the application raised questions about the reference to 'implicit consent' in the protocol because the IRB staff recognized that 'implicit consent' is not permitted by the IRB. An email provided to OHRP showed the conversation between the IRB staff and the study site to clarify what was meant by implicit consent in the protocol.

The site confirmed their plan to review the study information with the participants but [did] not obtain a signed consent form, which equates to a waiver of documentation of consent.

The reference to 'implicit consent' was used to describe a plan to waive the signature, not fully waive consent. The protocol contains the following:

'Attendance and participation in the focus group will be considered implicit consent by the parents and implicit assent by the teens. We will be requesting a waiver of consent documentation.'"

"Implicit Informed Consent" v. "Waiver of Consent"

"The reference to 'implicit consent' in the excerpt above did not require a full waiver as is traditionally understood using this term, rather the IRB ensured [that] the verbal consent script included all the required elements of a consent process and thus approved a waiver of documentation, not a full waiver.

The researcher confirmed that this phase of the study has been completed and that verbal consent/assent was obtained from practitioners and teens and their parents in the focus groups in accordance with the IRB approval.

For the pilot study portion of Phase I, full consent was obtained via a digital, online process from all participants (practitioners, parents, and teens).

The IRB approval letter does not specify that the IRB approved a waiver of consent applicable to this phase of the study since the process of 'implicit consent' represented a verbal consent procedure and thus required a waiver of documentation of consent, not a full waiver.

Regarding the presentation of key information at the start of the oral consent process, the brevity of the consent form enabled the text to meet the requirements of the key information and consent requirements together.

This approach is supported by details provided in the preamble to the Revised Common Rule for brief consent forms. This is consistent with BRANY's practice, but it is noted that the record did not document the determination.

IRB staff were provided with training on the requirements to clearly document discussions between the IRB and researchers. This training will also be reviewed with IRB members. Training materials will be provided to all IRB members and IRB staff." © {TBC}

FDA Warning

Warning Letter to: Ian Worden, MHA, MBA, CPO; Interim CEO, St. Vincent Health of Indianapolis, IN
Investigation Period: August 12, 2013, to August 23, 2013
Warning Letter Date: November 27, 2013
Noncompliance: IRB failure to follow two sets of federal regulations on protecting human subjects

* * *

IRB Fails to Follow Protection Rules for Pediatric Research

This IRB investigation was conducted by Myra Casey of FDA. The results were presented to Dr. Niceta C. Bradburn, the Interim Executive Director for Academic Affairs and Research for St. Vincent Health.

"1. The IRB failed to determine at the time of initial review that clinical investigations involving children were in compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations (21 CFR 56.109(h)) ....

Our inspection revealed that in its review and approval of 31 active clinical investigations involving pediatric subjects, the SVHHCC (St. Vincent Hospital and Health Care Center) IRB failed to determine that the clinical investigation satisfied the criteria of [21 CFR part 50] subpart D.

For example, on May 23, 2012, SVHHCC IRB reviewed and approved a pediatric clinical investigation titled '....' However, there is no documentation, either in the meeting minutes or in any other IRB materials, of the IRB's requisite determination at the time of initial review that the clinical investigation was in compliance with subpart D.

Your IRB's written response dated September 11, 2013, acknowledges the violation listed above and includes a copy of a 'Checklist for Research Involving Children.'

The checklist documents that, as a part of the IRB's corrective action plan, a subpart D review was performed for the above-mentioned pediatric clinical investigation and for two other pediatric clinical investigations (Studies ... and ...) that were included in the [investigation] Form FDA 483.

Your IRB's response also states that the IRB will perform a subpart D review for the remaining 28 of 31 active pediatric clinical investigations.

Your IRB's response is inadequate because it does not provide written assurance that a subpart D review has been completed for the remaining 28 active pediatric clinical investigations.

Failure to determine that the additional safeguards for children in research are met may expose this vulnerable population to unnecessary risks, and may result in the child's parent(s) or guardian(s) not being fully informed about the proposed research."

IRB Doesn't Use Routine IRB Membership Rules

"2. The IRB failed to fulfill membership requirements (21 CFR 56.107).

The IRB allowed nonmembers to vote on clinical investigations. Specifically:

a. IRB meeting minutes from March 28, 2012, show that an attendee identified as ... participated in voting. According to the IRB membership roster, Ms. ... was not a member of the IRB when this meeting was conducted.

b. IRB meeting minutes from June 29, 2011, show that an attendee identified as ... participated in voting. According to the IRB membership roster, Ms. ... was not a member of the IRB when this meeting was conducted ....

We acknowledge your IRB's September 11, 2013, written response, stating that several corrective actions have been implemented. These include the restructuring of the attendance grid of IRB meeting minutes, as well as training for IRB members on Standard Operating Procedure (SOP) #403, 'IRB Attendance Monitoring'; SOP #404, 'IRB Meeting Minutes'; and SOP #803, 'IRB Membership Addition.'

If properly implemented and executed, these procedures/actions appear adequate to prevent recurrence of similar violations in the future. Please ensure that the IRB is adhering to its SOPs, including fulfilling membership requirements and updating the membership roster ....

Within fifteen (15) business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Your written response should include any documentation necessary to show that full and adequate correction will be achieved.

Please include the projected completion dates for each action to be accomplished. Failure to explain the violations noted above adequately and promptly may result in regulatory action without further notice." ©

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IRB Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** Effective on ***May 2***, Angela Maria Giron, M.D., has been permanently debarred from:

"... providing services in any capacity to a person that has an approved or pending drug product application. FDA bases this order on a finding that ***Dr. Giron was convicted of a felony under Federal law for conduct relating to the development or approval, of any drug product*** .... [Dr. Giron] was a licensed physician and served as a clinical investigator at AMB Research Center, Inc. (AMB), a medical clinic located in Miami, Florida ....

AMB entered into a Clinical Trial Agreement with a Clinical Research Organization (CRO) that managed and oversaw a clinical trial designed to ***evaluate the safety and efficacy of an investigational drug*** intended to treat persons with Clostridium difficile-associated diarrhea (CDAD clinical trial) on behalf of a sponsor ....

For purposes of obtaining money from the Sponsor and/or CRO, ***Dr. Giron, along with her co-conspirators, created false and fraudulent study records***. For example, electronic case record files (eCRFs) falsely represented that the subjects completed the informed consent form (ICF) process, which required Dr. Giron to review the ICF with each subject and personally obtain the subject's written informed consent.

In truth and fact, ***Dr. Giron did not obtain written informed consent for any of the 22 subjects*** enrolled in the CDAD clinical trial ....

In addition, along with her co-conspirators, ***Dr. Giron falsified data of enrolled subjects*** in the CDAD clinical trial. For example, Dr. Giron did not conduct the required clinical investigator assessments at the second, third[,] and fifth [research subjects'] visits ....

Dr. Giron received $58,119.60 in proceeds for the CDAD clinical trial. AMB received more than $250,000 for the CDAD clinical trial" (89 Fed. Reg. 35836-35838 at p. 35837).

For details, contact: Jaime Espinosa of FDA's Office of Policy, Compliance, and Enforcement, at 240-402-8743, or send email to debarments@fda.hhs.gov.

• **Food and Drug Administration.** FDA is accepting comments ***until June 24*** regarding an information collection effort titled "Data to Support Social and Behavioral Research as Used by the Food and Drug Administration" (Docket No. FDA-2024-N-1055).

"This information collection is intended to support FDA-conducted research. Understanding patients, consumers, and healthcare professionals' perceptions and behaviors ***plays an important role in improving FDA's regulatory decision-making processes and communications*** that affect various stakeholders" (89 Fed. Reg. 30381-30383 at p. 30382, April 23).

For more information, contact: JonnaLynn Capezzuto of FDA's Office of Operations at 301-796-3794.

• **Food and Drug Administration.** FDA is accepting comments ***until June 25*** regarding a new public docket titled "Promoting Effective Drug Development: Identifying Opportunities and Priorities for the Food and Drug Administration's Office of Clinical Pharmacology."

"The purpose of this docket is to solicit input from interested parties on specific and actionable policy topics that could be prioritized, developed, and implemented by the staff of the Center for Drug Evaluation and Research (CDER's) Office of Clinical Pharmacology (OCP) ***to support effective drug development programs*** ....

Clinical pharmacology impacts many important aspects of drug development including, but not limited to, ... clinical trial [human subject] ***inclusion and exclusion criteria***, and evidence generation for ***safety*** and effectiveness determinations ....

Within CDER, OCP leverages clinical pharmacology information ... to ***support risk/benefit determinations*** ... for patients and practitioners" (89 Fed. Reg. 32444-32445, April 26).

For more information, contact: Anuradha Ramamoorthy of FDA's CDER at 301-796-1688.

• **National Institutes of Health.** NIH has announced that it is extending certain "flexibilities" in basic research that involve human subjects, aka "basic experimental studies with humans" (BESH). The relevant announcement is titled "Continued Extension of Certain Flexibilities for Prospective Basic Experimental Studies with Human Participants" (NIH Notice Number NOT-OD-24-118, May 6). In addition:

"***NIH also continues to expect posting of informed consent forms in accordance with NOT-OD-19-110 and as required by Section 446.116 (h) of the Revised Common Rule for all BESH that obtain informed consent.***"

For more information, contact: NIH Grants Information via email to grantsinfo@od.nih.gov. ©

IRB Compliance Conferences & Courses

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

• **June 18-20, 2024**: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP Virtual Conference."** This virtual course will be presented by the Society of Clinical Research Associates (SoCRA). The topics to be covered include: updates from FDA staff; the conduct of FDA inspections; what FDA expects in a pharmaceutical clinical trial; e-systems in clinical trials; special aspects of medical device research; operations and investigations of IRBs; FDA investigations of researchers; informed consent regulations; and oversight of decentralized clinical trials. Contact: Conference Registrar, SoCRA at 800-762-7292, or send email to Office@SoCRA.org, or see their Web site at www.SoCRA.org.

• **September 27-29, 2024,** in Las Vegas, Nevada: **"SoCRA Annual Conference -- Achieving Excellence in Clinical Research: Forging Strategic Collaborations."** This course will be presented by the Society of Clinical Research Associates (SoCRA). Meetings to be held at The Westgate Resort Las Vegas. Topics include: successes in using e-consenting, especially in community research; issues related to paying research participants; how to handle misconduct in clinical trials; operations of IRBs; strategies for successful recruitment of research subjects; the role of virtual tools in Human Ethic Committee (HEC) meetings; the ethics of pediatric biobanking; and the ethics of returning genetic test results to study participants. Contact: Conference Registrar, SoCRA at 800-762-7292.

• **September 29, 2024**: **"The Evolving Landscape of Human Research With AI - Putting Ethics to Practice."** This federal "Exploratory Workshop" will be livestreamed by the federal Office for Human Research Protections (OHRP), and registration is not required. The topics to be covered include: what unique risks AI poses for biomedical and social/behavioral research; how to prepare for and control these risks; how to conduct responsible and responsive AI research appropriately; possible regulations governing AI research; AI and personal privacy and identifiability of individual human subjects data; and how to guide future local and federal policy on the use of AI in research involving human subjects. Contact: Yvonne Lau, Ph.D., Director of Education and Development, OHRP, at 240-453-8236, or send email to yvonne.lau@hhs.gov.

• **December 5-6, 2024,** in Orlando, Florida: **"Emergency Clinical Research Symposium."** Meetings to be held at the Wyndham Lake Buena Vista. Topics include: emergency research regulations; the meaning of informed consent in emergency research; clinical trials involving pediatric participants; emergency research problems and solutions; and compassionate use and emergency use drugs in emergency research. This conference is presented by the Society of Clinical Research Associates (SoCRA). Contact: Conference Registrar, SoCRA at 800-762-7292, or send email to Office@SoCRA.org. ©

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.

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