America's Oldest National Monthly IRB Newsletter

Human Research Report™

PROTECTING RESEARCH SUBJECTS AND RESEARCHERS

Volume 39, No. 11 ISSN 0885-0615 November, 2024

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

IRBs and Long-Term Safety Studies In Neonatal Research Projects (#1)

Research with very young human subjects has always posed special protocol review challenges for IRBs. That situation is not changing. However, what is changing in an increased emphasis by FDA on using the results of long-term studies to inform future research in an effort to reduce risks for neonates who participate in very early research projects.

The relevant new guidance, containing numerous recommendations for IRBs and researchers, is titled "Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development: Guidance for Industry."

"This guidance is intended to provide a framework for considering whether and what type of long-term neurologic, sensory, and developmental evaluations could be useful in supporting a determination of safety of a FDA-regulated 'medical product' (i.e., drug, biological product, or medical device) for use in neonates" (89 Fed. Reg. 83892, October 18).

Research Requirements Part of Federal Law

"Although short-term safety evaluations may be appropriate for adults or other populations, such evaluations may not identify important adverse events in the neonatal population, as medical treatment during the neonatal period coincides with a time of critical growth and physiologic development and latent effects may not be evident until later in life following early-life exposures.

Consideration of the potential for long-term neurologic, sensory, and developmental effects in the neonatal population early in a development program is important for establishing safety of a medical product intended for use in neonates ....

Historically, most medical products used to treat neonates and young infants were not approved for use in these populations, and thus have not undergone comprehensive evaluation of safety or efficacy for use in neonates" (supra at pages 83820-83893).

The 11-page guidance contains a number of quite detailed issues for IRBs and associated researchers to consider when planning a research project with neonates.

"In 2012, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) were made permanent under Title V

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.

of the Food and Drug Administration Safety and Innovation Act (FDASIA). FDASIA contained several provisions to encourage medical product development in neonates" (guidance, October, p. 2; https://www.fda.gov/media/165239/download).

Possible Long-Term Harm to Subjects

"Clinical investigators and sponsors of neonatal studies should consider and assess potential short-term and long-term effects of an investigational therapy ....

Short-term clinical improvement, such as that observed after high-dose corticosteroids for infants with bronchopulmonary dysplasia, may be followed by unexpected long-term harm.

While adjunctive neurological assessments (e.g., neuroimaging, electroencephalography) may provide information on early safety concerns, they cannot replace clinical assessments of long-term functional outcomes.

Although there is no universal definition of 'long-term,' for the purpose of this guidance, the time frame can be generally thought of as at least 2 years of age or at such time when relevant clinical neurodevelopmental parameters can be reasonably assessed ...; the minimum duration of follow-up will depend on different population- and product-specific factors ....

Prospectively designed long-term follow-up is often important to understand medical product safety in neonates" (guidance at pp. 2-3).

Neonates Should Be Subjects in Studies Originally Designed for Older Subjects

"Neonates should have access to medical products adequately evaluated for safety, effectiveness, and, when appropriate, dosing for that population. There are conditions unique to term or preterm neonates, such as necrotizing enterocolitis and retinopathy of prematurity, that will not have analogous development programs in older populations.

As new medical products are developed for these and other unique neonatal conditions, novel development programs and first-in-human studies may be initiated in neonates, and these development programs should also demonstrate long-term neurologic, sensory, and developmental safety.

Neonates should also be enrolled in clinical studies for medical products and diagnostic tools initially developed in other populations that will be used for neonates. Inclusion of neonates in such studies may be useful to establish dosing, safety, and efficacy or effectiveness, and these studies may also warrant long-term safety evaluations" (supra at p. 3).

Special Study Design Issues for Neonates

"III. Neurodevelopmental Follow-Up for Product Development Programs That Include Neonates ....

Sponsors should communicate as early as possible with the relevant FDA review division to reach alignment on an appropriate approach for long-term safety evaluations.

A. Determining the Need for Long-term Neurodevelopmental Safety Evaluations

Sponsors should assess whether a long-term neurodevelopmental safety evaluation for neonates enrolled in clinical studies should be conducted. This assessment should be initiated early in product development and should be reevaluated as new information becomes available.

1. General Considerations

a. *Central Nervous System (CNS) Exposure*: Any route of administration may result in a systemic exposure. The degree of systemic exposure, which should be quantified in early pharmacokinetic or animal studies if possible, may inform the need for long-term safety assessment.

In general, higher levels of systemic exposure may be associated with higher CNS exposure and potential risk for long-term sequelae. The degree of CNS exposure may vary independently of systemic exposure.

b. *Timing of Exposure:* The timing of exposure to a drug, biological product, or device relative to a particularly vulnerable stage of organ and tissue development may inform the need for and the type of long-term safety assessment.

c. *Duration of Exposure:* Repeated dosing, prolonged exposure[,] and medical products with persistent effects may be associated with higher risk for long-term sequelae; however, long-term safety assessments may also be required after single doses or short durations of investigational therapies ...." (supra at pp. 3-4). © {TBC}

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

IRBs and Research With Decentralized Elements (#1)

A final FDA guidance contains several sections of immediate relevance for many IRBs and researchers. Titled "Conducting Clinical Trials With Decentralized Elements," the guidance:

> "... provides recommendations regarding the implementation of decentralized elements in clinical trials for drugs, biological products, and devices. Decentralized elements allow trial-related activities to occur remotely at locations convenient for trial participants (e.g., telehealth visits with investigators or visits with local healthcare providers (HCPs)) ....
>
> To help ensure the appropriate oversight of trials with decentralized elements, the integrity of trial data, and the safety of trial participants, this guidance covers the responsibilities of sponsors [including investigator-sponsors] and investigators" (89 Fed. Reg. 76481-76482, September 18).

IRB Oversight Is Required for DCTs

As we have discussed in previous HRRs, the COVID pandemic has significantly increased the use of "Decentralized Clinical Trials," or "DCTs." This development appears to be gaining momentum as researchers, and their associated IRBs, become more aware of new advantages to study results produced by DCTs.

> "Many clinical trials already include decentralized elements .... DCTs have the potential to expand access to more representative patient populations and improve trial efficiencies.[7]
>
> [FN #7: See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations -- Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020) ....]
>
> Advances in using electronic communications and information technology to interact with trial participants in different locations (i.e., telehealth) allow for fewer in-person visits to traditional clinical trial sites. **Digital health technologies** (**DHTs**), for example, have expanded the types of trial-related data that can be obtained remotely from trial participants.
>
> By enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, and facilitate research on rare diseases and diseases affecting populations with limited mobility or limited access to traditional clinical trial sites.
>
> This may help improve trial participant engagement, recruitment, enrollment, and retention of a more representative trial participant population to improve the strength and generalizability of the evidence produced by the trial" (guidance, September, p. 2 of 18).

Of the guidance's sections most relevant for IRBs, we begin with the section titled **"F. Informed Consent and Institutional Review Board Oversight."**

> "Obtaining informed consent remotely may be considered as part of a DCT. Institutional Review Board (IRB) oversight is required to ensure [that] the process is adequate and appropriate.
>
> • Investigators may obtain informed consent (either electronically or on paper) from trial participants at their remote locations provided that all applicable regulatory requirements are met[38]" (supra at p. 12).

Agency Recommends Use of a Central IRB

> "[FN #38: For FDA regulations about informed consent, see 21 CFR part 50 (including the elements of informed consent under 21 CFR 50.25 and the documentation of informed consent under 21 CFR 50.27).
>
> For additional information, see the guidance for IRBs, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (Dec. 2016). See also the guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (Aug. 2023).]
>
> The process of obtaining informed consent from participants at their remote locations can include a remote visit .... If the investigator delegates this responsibility, the individual obtaining informed consent should, among other things, have a detailed knowledge of the protocol and have the appropriate training and credentials to be able to address any questions or concerns the subject may have about the trial.
>
> FDA therefore does not consider obtaining informed consent to be an appropriate activity for a local HCP to perform.
>
> • With a DCT, the informed consent process must include notifying participants (or their legally authorized representatives) of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject in accordance ....
>
> • When appropriate, FDA recommends the use of a central IRB in DCTs to facilitate efficient review of the protocol ... [and] the informed consent documents" (ibid). © {TBC}

IRBs and Research With LGBTQI+ Subjects (#3)

We continue now with more IRB recommendations from the document titled "SACHRP Recommendations for the Ethical Review and Inclusion of LGBTQI+ Participants in Human Subjects Research."

"Ensuring the equitable inclusion of LGBTQI+ participants in research is essential for safeguarding their rights and welfare. As with research involving other underrepresented groups and study populations, investigators, sponsors, IRBs/HRPPs, and research institutions must adhere to the ethical standards outlined in the BELMONT REPORT and incorporated in applicable agency guidelines and federal regulations (e.g., HHS regulations at 45 CFR part 46 and the FDA Regulations at 21 CFR parts 50 and 56, etc.)" (SACHRP Recommendations, July 24, p. 6; on the Web at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/ethical-review-inclusion-lgbtqi-participants-human-subjects-research/index.html).

Adding Subjects as "After Thought" Usually Fails

"This includes actively considering how research decisions, such as recruitment methods and data collection practices, affect the inclusion, privacy, and safety of LGBTQI+ participants in research.

Promoting a scientifically inclusive evidence base demands the alignment of research priorities and research resources with the needs and concerns of LGBTQI+ individuals and communities. Efforts to achieve fairness in the goals, conduct, and impact of research concerning LGBTQI+ populations require recognition of how the current research enterprise needs to improve its efforts to properly identify these populations and tailor study aims and methods appropriately.

Inclusion as an afterthought consistently fails. Instead, planning and collaboration across stakeholder groups, from IRBs/HRPPs, sponsors, research institutions, investigators, regulatory bodies, and those with lived experience is needed to best serve the needs and concerns of LGBTQI+ communities.

Applying these principles and assessing whether research addresses topics relevant to and inclusive of LGBTQI+ communities is important because, according to a 2022 report from the National Academies of Sciences, Engineering, and Medicine (NASEM), there are 'major knowledge gaps [regarding] the health needs of [LGBTQI+] people. Research often fails to collect [such] data.'

The NASEM report also identified multiple threats stemming from underrepresentation in research, including the risk that research results may not be generalizable to underrepresented participants, preventing them from receiving the benefits of research which may result in negative health effects and economic costs.

Such outcomes are inconsistent with the three Belmont principles -- *respect for persons*, *beneficence*, and *justice* -- which are the foundation for applicable agency guidelines and federal regulations. LGBTQI+ individuals are underrepresented in research while this underrepresentation is not as thoroughly documented as it is for racial or ethnic populations" (supra at pp. 6-7).

IRBs Have Duty to Support Inclusion

"The underrepresentation of LGBTQI+ communities limits their access to potential direct and indirect research benefits. It also further marginalizes such individuals by failing to sufficiently recognize and include them. As a result, they may face a number of barriers to healthcare and other non-healthcare related services.

It is therefore incumbent on investigators, sponsors, IRBs/HRPPs, and research institutions to take steps toward more ethical and inclusive research and eliminate these disparities. Ensuring fairness in access requires awareness of the social and cultural circumstances particular to LGBTQI+ groups (and subgroups within these communities), and the thoughtful and informed identification of risks specific to these groups.

Investigators, sponsors, IRBs/HRPPs, and research institutions should recognize and respect the complexity of LGBTQI+ participants' identities, ensuring that studies consider intersecting factors such as race, ethnicity, age, disability, socioeconomic status, and other factors.

Evidence demonstrates that engaging with various communities and having diverse representation within research institutions fosters more respectful and inclusive research that addresses LGBTQI+ needs and concerns and builds trust.

Failure to tailor research to support the inclusion of individuals with diverse gender identities and sexual orientations also maintains and creates gaps in the evidence base. Including these individuals may provide preliminary information or signals regarding efficacy and harm, even when participant numbers do not allow for statistically sound subgroup analysis." © {TBC}

IRBs and Digital Health Technologies (#3)

We continue this month with more recommendations for IRBs reviewing the research protocols of studies involving any Digital Health Technology (DHT). We resume with the concluding portion of the relevant FDA's guidance section related to human subjects titled "*2. Privacy-Related Risks*."

> "-- To protect data privacy for trial participants, it may be appropriate for sponsors to proactively work with manufacturers to modify the end-user license agreement or terms of service for the purposes of the study, as applicable.
>
> • Sponsors should ensure that appropriate security safeguards are in place to secure data at rest and in transit to prevent access by intervening or malicious parties (e.g., cybersecurity threats)" ("Digital Health Technologies [DHTs] for Remote Data Acquisition in Clinical Investigations: Guidance for Industry, Investigators, and Other Stakeholders," December, 2023, p. 19 of 32; on the Web at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations).

When Electronic Informed Consent Is Used

"*3. Informed Consent*

FDA regulations at 21 CFR part 50 set forth the requirements for obtaining the informed consent of participants in clinical investigations. DHTs can be used to obtain electronic informed consent in a clinical investigation.[60]

> [FN #60: See the guidance for IRBs, investigators, and sponsors *Use of Electronic Informed Consent in Clinical Investigations: Questions and Answers* (December 2016). See also the guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (Aug. 2023), section V, question 10 regarding electronic informed consent.]

Some considerations for what information to include in the informed consent process regarding the DHT being used in a clinical investigation include but are not limited to the following:

• The informed consent process must describe any reasonably foreseeable risks or discomforts to participants (see sections IV.F.1 and IV.F.2 of this guidance), including reasonably foreseeable risks or discomforts related to the use of the DHT in the clinical investigation.

Information regarding what may be done to mitigate serious risks, and risks and discomforts more likely to occur, should also be considered for inclusion.

• When appropriate, a statement must be included indicating that use of the DHT during the clinical investigation may involve risks to the participant (or to the embryo or fetus if the participant is or may become pregnant) which are currently unforeseeable.

• The informed consent process should explain the type of information that will be collected by the DHT and how that information will be used and monitored. When relevant, participants should be informed of what action to take in case of any concerning sign, symptom, or abnormal clinical event (e.g., hypoglycemia or abnormal cardiac rhythm) detected by a DHT, such as seeking emergency medical attention, if appropriate" (supra at pp. 19-20).

"Access to Data" Is Particularly Sensitive Issue

"• The informed consent process should specify who may have access to data collected through the DHT during or after the clinical investigation (e.g., sponsors, investigators, participants, DHT manufacturers, other specified third parties) and during what time frame.[63]

> [FN #63: In addition, the informed consent process must note the possibility that FDA will inspect records identifying the participants (21 CFR 50.25(a)(5)).]

• An explanation of measures to protect participant privacy and data, and limitations to those measures, when DHTs are used should be included.

• If participants may incur additional expense because they are taking part in the clinical investigation, the consent process must explain the added costs, which could include costs for the participants that may result from using the DHT during the clinical investigation (e.g., data use charges).

• DHTs or other technologies may be covered by end-user license agreements or terms of service as a condition of use, which may, among other things, allow DHT or other technology manufacturers and other parties to gain access to personal information and data collected by the DHT or other technology.

When applicable, sponsors and investigators should ensure that the informed consent process explains to participants that their data may be shared outside of the clinical investigation, according to the end-user license agreement or terms of service" (supra at pp. 20-21). © **{TBC}**

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

IRBs and Patient-Reported Outcomes in Cancer Trials (#1)

We continue this month with more recommendations for IRBs regarding an area that didn't even exist a few years ago; namely, the use of "patient-reported outcomes" (PROs) in cancer clinical trials. Of course, the opinions and experiences of human subjects in such research have been helpful to researchers in the past.

However, assessment of efficacy and other research results have usually been restricted to statistical measures and directly observable outcomes. The situation is quite different with the advent of the use of PROs and the IRB protocol reviews involved with such studies.

We find that a new final guidance from FDA, titled "Core Patient-Reported Outcomes in Cancer Clinical Trials," provides useful advice for applicable IRBs considering PROs in protocols.

> "This final guidance provides recommendations to sponsors regarding the collection of a core set of patient-reported clinical outcomes … in cancer clinical trials and related considerations for instrument selection and trial design" (89 Fed. Reg. 83884, October 18).

Benefit/Risk Assessments and PROs

> "This final guidance focuses on patient-reported outcome (PRO) measures and is specific to registration trials for anti-cancer therapies intended to demonstrate an effect on survival, tumor response, or delay in the progression of a malignancy ….
>
> FDA acknowledges the added value of incorporating PRO measurement of symptoms and functional impacts into the benefit/risk assessment in appropriately designed trials; however, heterogeneity in PRO assessment strategies has lessened the regulatory utility of PRO data from cancer trials.
>
> Systematic assessment of a core set of PROs can facilitate high-quality data on patient-reported symptoms and functional impacts. In published literature, FDA authors have previously described a core set of PROs that may be important contributors to a patient's health-related quality of life and that may be sensitive to the effect of the disease and treatment under study" (supra at page 83885).

So exactly what does an IRB look for in a relevant cancer trial protocol review?

> "Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer, a performance-based assessment, or through other methods.
>
> A PRO measure is a type of clinical outcome assessment (COA) based on a report that comes directly from the patient about the status of a their health condition without amendment or interpretation of the patient's response by a clinician or anyone else.
>
> Additional definitions of patient-focused drug development terms can be found in the Patient-Focused Drug Development Glossary.[4]
>
> [FN #4: Available at https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary ...]" (guidance, October, p. 2; on the Web at Docket FDA-2020-D-2303).

The Types of PROs for IRBs to Consider

> "Cancer trials typically employ standardized efficacy assessments using overall survival and tumor measures, and safety assessments provided by clinician reporting of adverse events ….
>
> [In contrast, however] A core set of PROs that may be important contributors to a patient's health-related quality of life (HRQOL) and that may be sensitive to the effect of the disease and treatment under study has been described in published literature.[6]
>
> [FN #6: Kluetz PG, Slagle A, Papadopoulos E, et al., 2016, Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms, Clin Can Res, Apr 1;22(7):1553-8.]
>
> To maximize the regulatory utility of submitted PRO information, we recommend collecting and separately analyzing the following core PROs:
>
> - Disease-related symptoms
> - Symptomatic adverse events
> - Physical function
> - Role function
>
> Additional PROs that are important to patients, outside of the core concepts in this section, could be prospectively specified and collected in clinical studies based on the context of a given clinical trial.
>
> For instance, swallowing function and cognitive function may be outcomes of interest in addition to the core set in the context of advanced esophageal cancer and neuro-oncology, respectively.
>
> Selection of outcomes outside of the core PRO set should be carefully considered to minimize patient burden and improve the quality of data collected by focusing on the most meaningful and measurable outcomes" (pp. 2-3). © {TBC}

IRBs and Integrating Randomized Trials (#1)

A new draft FDA guidance poses unusual challenges for affected IRBs. The challenges arise due to the blending of both experimental factors and nonexperimental clinical practice features into one overall process.

The guidance is titled "Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice."

> "This draft guidance is intended to support the conduct of randomized controlled drug trials with streamlined protocols and procedures that focus on essential data, allowing integration of research into routine clinical practice.
>
> Depending on the condition and the intervention to be studied, the spectrum of trial designs may range from those that are almost completely reliant on data acquired by the participant's local healthcare providers during routine clinical practice visits to those that require significant supplementation with dedicated, research-specific activities for data collection conducted by trial staff" (89 Fed. Reg. 76482-76484 at p. 76483, Sept. 18).

Informed Consent Always Necessary

> "As part of FDA's Real-World Evidence (RWE) Program, this guidance is intended to support the conduct of randomized controlled drug trials (RCTs) with streamlined protocols ... [that] have sometimes been referred to as *point of care trials or large simple trials*.
>
> Like decentralized clinical trials, which aim to bring trial-related activities to patients' homes or other convenient locations, such RCTs may improve convenience and accessibility for participants and allow for enrollment of more representative populations, resulting in more generalizable trial results.
>
> Leveraging established health care institutions and existing clinical expertise in the medical community can reduce startup times and speed up enrollment" (guidance, September, p. 1 of 13; on the Web at https://www.fda.gov/media/181871/download).

There are several sections of the guidance that we find to be of particular relevance for IRBs. For example, the brief section titled "**B. Obtaining Informed Consent**" states that:

> "There are various regulations regarding human subject protection and oversight by institutional review boards that are applicable when conducting a trial, including a trial integrated into clinical practice. Investigators must generally obtain informed consent from participants in a clinical trial, consistent with the requirements in 21 CFR part 50, and ensure that an institutional review board that complies with the requirements in 21 CFR part 56 will oversee the clinical study.
>
> In addition, because protected health information may be part of trials, including those conducted in clinical practice, investigators should consider any additional requirements that may be relevant under the Health Insurance Portability and Accountability Act of 1996 (HIPAA)" (supra at pp. 8-9).

Collection of Safety Data May Be Necessary

Human subject safety has always been a hallmark of IRBs' duties and functions. Hence, it is no surprise that the guidance's section titled "**C. Choosing Suitable Investigational Drugs**" contains tips useful for applicable IRBs active in this area.

> "Drugs that are already FDA-approved for an intended use have better established safety profiles and are generally more suitable for use in trials integrated into clinical practice than drugs that are unapproved for any use.
>
> An approved product's well-characterized safety profile for the approved use may mean that limited collection of safety data for the unapproved use may be appropriate in certain circumstances.
>
> For example, when using an FDA-approved drug, it may be appropriate to consider selective collection of safety data, such as serious adverse events, adverse events of special interest, and adverse events that lead to discontinuation of the drug or withdrawal from the trial without the need to collect nonserious adverse events that are already well characterized.[29,30]
>
> [FN #29: See the guidance for industry *Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations* (February 2016).
>
> FN #30: See the ICH [International Conference on Harmonisation] guidance for industry *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials* (December 2022).]
>
> Sponsors should consult with the relevant FDA review division to determine whether a selective approach to safety data collection would be appropriate" (supra at p. 9).

Comments on the guidance are due by December 17. More information is available from Heather Stone at 301-796-2274. © {TBC}

IRBs and Final Rule on Research Misconduct

Cases of research misconduct can involve IRBs in initial stages, although such events are then usually handled by misconduct committees or similar bodies at research institutions. Sometimes, however, the individual(s) who deal with human subject protections also address research misconduct situations.

There are occasions when misconduct rules and human subject protection rules can overlap in part -- especially if human subjects' safety or privacy is concerned -- even if IRBs do then refer subsequent formal responses to other colleagues for appropriate reactions.

Therefore, we suggest that IRBs at least be familiar with the current misconduct regulations. The new final version of the Public Health Service Policies on Research Misconduct (42 CFR Part 93) was published in 20 pages of the September 17 FEDERAL REGISTER (pp. 76280-76309) in 3-columned small print text. The details are extensive.

> "**§93.234 Research misconduct.**
>
> Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results ...." (p. 76300).

Applicable Research Activities Cover Many Areas

Note that human subject privacy continues to be a concern for IRBs, and any related misconduct violations could be covered in the following definition of what is addressed by the regulations:

> "**§93.236 Research record.**
>
> Research record means the record of data or results that embody the facts resulting from scientific inquiry. Data or results may be in physical or electronic form.
>
> Examples of items, materials, or information may be considered part of the research record include, but are not limited to, research proposals, raw data, processed data, clinical research records, laboratory records, study records, laboratory notebooks, progress reports, manuscripts, abstracts, theses, records of oral presentations, online content, lab meeting reports, and journal articles" (ibid).

The newly issued final rule comes after years of development and changes to previous versions.

> "The final rule reflects both substantive and non-substantive revisions in response to public comments and to improve clarity. The purpose of the final rule is to implement policy changes and respond to technological changes [e.g., artificial intelligence, or 'AI'] that occurred over the past several years applicable to research misconduct" (supra at p. 76280).

Before continuing with our coverage highlights, we add that this final rule becomes effective on January 1, 2025. For more information, contact: Justina Lawrence at 240-453-8200.

Privacy of Charged Researchers Is Put Back

As noted above, the Health and Human Services (HHS) Office of Research Integrity (ORI) received numerous comments over the years with many suggested changes to misconduct regulations. One change urged by members of the research compliance community involves possible publicity about findings of misconduct at research institutions. Hence:

> "Many commenters urged ORI to remove §93.410(b), which proposed that ORI publish notice of institutional investigations and actions. Commenters cited regulatory overreach, breaches of confidentiality, and inconsistency with other agencies' policies.
>
> One commenter noted that ORI's publication of institutional reports and findings would be inconsistent with the confidentiality provisions established in the clinical research context.
>
> A minority of commenters recommended revising the section to redact respondents' identify ing information to ensure confidentiality. A few commenters recommended retaining the section as proposed.
>
> ORI removed proposed §93.410(b) from the final rule, ensuring [that] institutions [will continue to] have discretion in this area" (p. 76286).

What about situations in which misconduct charges are alleged, but are not supported by resultant investigations?

> "Proposed §93.304 regarding institutional policies and procedures removed a provision that was in the 2005 regulation requiring institutions to have policies and procedures in place to protect the rights of respondents.
>
> Commenters were concerned about protecting these rights and ORI restored the language from the 2005 regulation that institutions provide for all reasonable and practical efforts, if requested and as appropriate, to protect or restore the reputation of persons alleged to have engaged in research misconduct but against whom no finding of research misconduct is made" ("Subpart C - Summary of Significant Public Comments and Changes," supra at p. 76281). © **{TBC}**

OHRP Investigation of IRBs and Researchers

Project Title: Human Research Protections Under Federalwide Assurance No. 0935 (Leland Stanford Junior University, Stanford, California) (*Part #2*)

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

Allegations: A not-for-cause investigation of the University's IRBs and their activities.

Reference: OHRP letter of September 16, 2022, to Kathryn A. Moler, Ph.D., Vice Provost and Dean of Research; from OHRP's Crystal M. Kelly, MPH, Compliance Analyst, Division of Compliance Oversight

* * *

Stanford Must Make Changes to IRB Procedures

We continue now with more of the investigation dialog between Stanford and OHRP. We resume with the rest of the university's "response" to OHRP's concern that Stanford's IRB might not be able to discern when certain "incident" reports had to be filed with OHRP, with FDA, or with both.

> "**[Response ...]** The IRB determines whether the incident occurred in non-exempt human subjects research and is an unanticipated problem involving risks to subjects or others, serious or continuing noncompliance, suspension, and/or termination of IRB approval.
>
> The [Stanford] HRPP Policy Manual has been updated to be more explicit about Stanford's process for reporting incidents to OHRP.
>
> **[OHRP Finding]** During our evaluation, it appeared your processes were generally compliant with the 2018 Common Rule requirements. However, OHRP noted that Stanford's IRB written procedures and guidance documents did not appear to reflect the 2018 Common Rule requirements, such as the waiver or alteration of consent requirements, the waiver of documentation of consent requirements, the reporting requirements, and the exempt research criteria.
>
> **Response**: Stanford has made the noted updates to the HRPP Policy Manual, guidance documents, and the IRB's eProtocol system to reflect the 2018 Common Rule requirements.
>
> **[OHRP Finding]** During the IRB meetings that OHRP observed, some discussions of risk appeared to rely on a 'low, medium or high' risk categorization, the relationship of which was unclear to the Common Rule's definition of minimal risk (45 CFR 46.102(j)). A similar observation was noted for assessments and documentation of risk within eProtocol.
>
> **Response**: According to your response, the low/medium/high designation that prompted OHRP's question is intended for Stanford's internal institutional purposes, such as categorizing the study in case Risk Management needs to understand the relative risk that a study might pose for institutional coverage and liability exposure.
>
> Furthermore, Stanford has updated its approval letters and eProtocol system to reflect terms consistent with the risk levels specified in the Common Rule."

Confusion Over Applicability of FDA's IRB Rules

> "**[OHRP Finding]** During the records review, OHRP noted that the eProtocol system only allowed one regulation to be selected for a waiver of documentation of consent when more than one regulation may apply. For studies under both HHS and FDA's jurisdiction, only the FDA regulation was selected.
>
> **Response:** According to your response, Stanford modified eProtocol to allow selection of applicable regulatory requirements waiving documentation of consent under both FDA and HHS regulations. This change allows clearer documentation that the determinations are in fact being made under the applicable regulations for both HHS and FDA.
>
> **[OHRP Finding]** The General Requirements for Informed Consent guidance document (GUI03C41) stated, 'Common Rule general requirements, basic elements, and additional elements of consent do not apply to FDA regulated research because the FDA has not yet harmonized with the revised OHRP regulations at 45 CFR 46.'
>
> This could appear to be saying that the elements of consent in the revised Common Rule were not required for FDA regulated studies, even when the research is HHS funded or supported.
>
> **Response**: According to your response, Stanford updated this guidance document to reflect that Common Rule requirements for consent apply to FDA regulated studies that are also subject to the Common Rule." © {TBC}

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

FDA Warning

Warning Letter to: William C. Domb, DMD, Chair, Inland Institute of Aesthetic Dentistry Institutional Review Board; Upland, California *(Part 3)*
Investigation Period: September 23, 2014, to October 16, 2014
Warning Letter Date: May 13, 2015
Noncompliance: IRB failure to comply with seven areas of human subject protection regulations; restrictions imposed, including cessation of enrolling new subjects

* * *

A New Kind of "Very Short Form" for Consent

We resume here with more of the violations committed by the IRB in question, beginning with the fourth area of the IRB's noncompliance.

"4. Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. (21 CFR 50.25(a) and 56.109(b))

In seeking informed consent, basic elements, and additional elements when appropriate, must be provided to each subject as described in 21 CFR 50.25 (see also 21 CFR 56.109(b)).

The IRB failed to adhere to these requirements. Specifically, the informed consent documents (ICDs) for the study titled, ... did not adequately address all eight of the basic elements of informed consent .... For example, the ICDs did not include:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that FDA may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."

IRB Must Explain How It Will Start Complying

"Moreover, it is unclear whether informed consent was documented by the use of a written informed consent form approved by the IRB in accordance with 21 CFR 50.27 where IRB members allegedly approved ICDs [informed consent documents] over the phone or by email for the study.

A valid informed consent process ensures that research subjects have a clear understanding of risks of participation in a research protocol, have sufficient opportunity to consider whether to participate in the study, and make an informed decision if they decided to participate.

The elements omitted from the ICDs include important information such as the risks and benefits of participating in the study, the extent of the subject's confidentiality, the subject's financial burden while participating in the study, important contact information, and statements that the subject is participating in experimentation voluntarily.

Study subjects are required to have this information prior to study enrollment. By failing to require the use of appropriate ICDs before enrolling subjects in a clinical investigation, the IRB did not adequately protect the rights and safety of those human subjects.

In the IRB's response, you state that you will ensure that the IRB will approve only those ICDs containing the required elements.

This response is inadequate because it lacks sufficient detail to ensure that the IRB will do so." © {TBC}

IRB Compliance Comment Deadlines & Notices

• **Food and Drug Administration.** Comments are ***due by December 17*** on a new draft guidance titled "Postoperative Nausea and Vomiting: Developing Drugs for Prevention" (see Docket FDA-2024-D-3993-0002).

"This guidance provides ***recommendations regarding the design of clinical trials*** for the prevention of postoperative nausea and vomiting in adults, including considerations for ***eligibility criteria***, trial design features, efficacy evaluations, and ***safety assessments*** ….

Postoperative nausea and vomiting (PONV) is a serious, common, and distressing complication of surgery occurring within the 0- to 24-hour postoperative period in approximately 30 percent of the general surgical population and increasing to as high as 80 percent in high-risk cohorts.

Nausea and vomiting following surgery can cause serious complications, including electrolyte imbalances and dehydration, ***can have a significant impact on how patients are functioning, and may prolong hospitalization and recovery from surgery***.

Additional complications of uncontrolled PONV can include esophageal tears, wound dehiscence, and decreased self-care and functional ability" (89 Fed. Reg. 83881, October 18).

Due to the relevance of much of this guidance for IRB protocol reviews, and the widespread applicability of the guidance to numerous biomedical disciplines, ***we plan to excerpt key portions in future HRRs***.

For more information, contact: Mary Chung of FDA's CDER at 301-796-0260.

• **Food and Drug Administration.** The final version has been released of "Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers."

"The guidance provides information for sponsors, clinical investigators, ***institutional review boards (IRBs),*** contract research organizations (CROs), and other interested parties on the use of electronic systems, electronic records, and electronic signatures in clinical investigations of foods, medical products, tobacco products, and new animal drugs.

The guidance provides recommendations regarding the requirements in our regulations, pursuant to which FDA considers electronic systems, electronic records, and electronic signatures to be trustworthy, reliable, and ***generally equivalent to paper records and handwritten signatures executed on paper.***" (89 Fed Reg 80255, Oct. 2l).

There were changes to seven different areas covered in the previous draft version (based on feedback from IRB members, in part), in addition to editorial changes to "improve clarity." The 25-page guidance is available on the Web at https://www.fda.gov/media/166215/download.

For more information, contact: Elizabeth Kunkoski of FDA's CDER at 301-796-6439, or send email to Elizabeth.Kunkoski@fda.hhs.gov.

• **Secretary's Advisory Committee on Human Research Protections.** The SACHRP scheduled a ***meeting for October 22*** as a webcast.

"Julie Kaneshiro [the current Acting Director of OHRP] will introduce Dr. Molly Klote, newly appointed Director of OHRP. Dr. Douglas Diekema, SACHRP Chair, will make opening remarks. The meeting will begin with a discussion of the draft recommendation, ***Considerations for Uninformative Research***.

This will be followed by panel presentations and discussion of a new SACHRP topic on ***Equivalent Protections and Procedural Requirements in International Research"*** (89 Fed. Reg. 83895, October 18).

For more information, contact: Julia Gorey, J.D., Executive Director, SACHRP, at 240-453-8141, or send email to SACHRP@hhs.gov.

• **Secretary's Advisory Committee on Human Research Protections.** The federal charter for the SACHRP was renewed on October 1 for two more years, until October 1 of 2026.

"SACHRP functions to provide advice to the ... Assistant Secretary for Health, on matters pertaining to the ***continuance and improvement of functions within the authority of the Department of Health and Human Services concerning protection for human subjects in research***.

SACHRP is authorized to have 11 public voting members. The members are selected from among individuals possessing demonstrated experience and expertise in any of the several disciplines and fields pertinent to human subjects protection and/or clinical research. The Committee's public members are appointed by the Secretary" (89 Fed. Reg. 80575, October 3).

For details, contact: Julia Gorey, J.D., Executive Director, SACHRP, at 240-453-8141. ©

IRB Compliance Conferences & Courses

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

• **November 6-7, 2024, in New Orleans, Louisiana**: **"FDA Clinical Trial Requirements, Regulations, Compliance, and GCP Conference."** Conference is presented by SOCRA, with meetings to be held at the Sheraton New Orleans Hotel. The topics include: updates from FDA staff; details on FDA inspections; FDA's GCP compliance reviews for NDAs and BLAs; changing ethical principles and how they apply to current clinical trials; how to structure proactive compliance in a research program; how FDA investigates researchers; IRB regulations; and dealing with electronic records. Contact: Conference Registrar, SoCRA at 800-762-7292.

• **November 17-20, 2024,** in Seattle, Washington: **"PRIM&R 2024 Annual Conference."** The numerous workshops, seminars, panels, poster sessions, exhibitors, and other continuing education offerings make this **THE** annual conference to attend each year. For example, this year's **50th anniversary** topics include: advancing equity and justice in research; updates from federal agency staff; fda-regulated research regulations; HRPP and IRB administration and management; IRB fundamentals and protocol review procedures; informed consent; legal considerations in research oversight; vulnerable populations requiring additional protections; QA/QI and postapproval monitoring of human subjects studies; challenges faced by single IRBs reviewing multiple study sites; regulatory issues in social, behavioral, and educational research; CIP accreditation; emerging research challenges; federal agency updates; FDA's sIRB mandate; online training in human subjects protections; special considerations for subjects with developmental disabilities; research subject data and biospecimen sharing with privacy concerns; using controlled substances in research; using research subject experience data; current and future single IRB (sIRB) requirements; cybersecurity; measuring capacity to consent to research participation; gender inclusivity in subject enrollment; and too many other topics to list here. Contact: PRIM&R at 617-423-4112, or email to info@primr.org, or see their Web site at www.primr.org.

• **December 5-6, 2024,** in Orlando, Florida: **"Emergency Clinical Research Symposium."** These SOCRA meetings will be held at the Wyndham Lake Buena Vista. Topics include: emergency research regulations, and the meaning of informed consent in emergency research. Contact: SoCRA at 800-762-7292.

• **December 5-6, 2024, in Orlando, Florida**: **"Clinical Research Nursing Conference."** Meetings to be held at the Wyndham Garden Lake Buena Vista. Topics include: the role of clinical research nurses as research subject advocates; how the protection of human research subjects impacts nursing studies; and the regulations and procedures that promote safe and ethical research studies. 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.

Gold Member Since 1993 BBB

BBB Rated as A+ ("Excellent")

The HUMAN RESEARCH REPORT is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold with the understanding that the publisher (The Deem Corporation) is not engaged in rendering legal, accounting, or other professional service.

If legal advice or other expert assistance is required, then the services of a competent professional should be sought. Preceding statement from a Declaration of Principles jointly adopted by a Committee of the American Bar Association and a Committee of Publishers.

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

2025 Subscription Prices*

$189 per year for 12 monthly emailed copies for the **First Subscriber**

Only $19 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