HCCA Research Compliance Conference

Hot FDA Compliance Issues for 2022

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What We Will Cover

- Who at FDA primarily oversees medical device research?
- What are recent FDA policy initiatives affecting compliance in medical device research?
- What are recent clinical and non-clinical research violations triggering compliance actions?
- What should you do to meet FDA expectations and avoid regulatory problems in your medical device research efforts?

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PRIMARY OVERSIGHT

- FDA's bioresearch monitoring program was established in 1977 by a task force.
- The FDA task force included representatives from the drug, biologics, medical device, veterinary medicine, and food areas.
- The need for such a program was evident in a survey of the conduct of studies involving FDA-regulated products by the FDA field inspection operations between 1972 and 1974.
- Following a review of the survey findings, Congress mandated that FDA develop and implement an agency-wide program.

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PRIMARY OVERSIGHT

- Presently the CDRH Office of Clinical Evidence and Analysis (OCEA) monitors sponsors, institutional review boards, clinical investigators, and nonclinical laboratories involved in the testing of investigational devices.
- OCFA is within CDRH's Office of Product Evaluation and Quality (OPEQ)
- It provides policy and program support regarding clinical trials, biostatistics, real-world evidence, epidemiological analysis and outreach and collaboration with hospitals and other external stakeholders.
- It wears several different "hats"

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OCEA OVERSIGHT

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- Provides policy and program support for clinical evidence and human subject protection.
- Supports device reviews that require expert clinical investigation and real-world evidence analysis.
- Provides regulatory oversight of medical device clinical investigations, good laboratory practice (GLP), and good clinical practice (GCP) issues.
- Provides biostatistical and epidemiologic analyses, as well as support in the development of data infrastructure and expertise on clinical investigations and real-world evidence.

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OCEA OVERSIGHT

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- Provides programmatic support for Offices of Health Technology (OHTs) engaging in total product life cycle review of devices.
- Conducts outreach and collaboration with hospitals and other external stakeholders.

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RECENT POLICY INITIATIVES

- FDA issued a draft guidance document entitled "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations: Guidance for Industry, Investigators, and Other Stakeholders"
- It issued in December 2021
- In the guidance, FDA defines a "digital health technology" (DHT) as a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses.

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RECENT POLICY INITIATIVES

- The guidance provides recommendations for sponsors, investigators, and other interested parties on the use of DHTs for remote data acquisition from participants in clinical investigations evaluating medical products.
- It outlines recommendations intended to facilitate the use of DHTs in a clinical investigation for the evaluation of medical products.

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RECENT POLICY INITIATIVES

- These recommendations address information that should be contained in an Investigational New Drug application (IND) or an Investigational Device Exemptions (IDE) application for a clinical investigation in which the sponsor plans to use DHTs.
- It also addresses such information for a marketing application that includes data from a clinical investigation using DHTs.

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RECENT POLICY INITIATIVES

- More specifically, these recommendations address the following topics:
- Selection of DHTs that are suitable for use in the clinical investigation
- Verification and validation of DHTs for use in the clinical investigation

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RECENT POLICY INITIATIVES

- Use of DHTs to collect data for trial endpoints
- Identification of risks associated with the use of DHTs during the clinical investigation
- Management of risks related to the use of DHTs in clinical investigations

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RECENT POLICY INITIATIVES

- FDA issued a draft guidance document entitled "Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices: Draft Guidance for Industry"
- It issued in September 2021
- FDA intends the draft guidance to help clinical investigators comply with the safety reporting requirements.

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RECENT POLICY INITIATIVES

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- These safety reporting requirements are found as follows:
  - At 21 C.F.R. 812.150 for Investigational Device Exemption studies
  - At 21 C.F.R. § 312.64(b) for Investigational New Drug Application studies

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RECENT POLICY INITIATIVES

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- Recommendations are provided to help investigators identify the following:
  - For devices — Identify safety information that meets the requirements for reporting unanticipated adverse device effects to sponsors and IRBs
  - For drugs — Identify safety information that is considered an unanticipated problem involving risk to human subjects or others and that therefore requires prompt reporting to IRBs

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RECENT POLICY INITIATIVES

- The guidance also provides relevant information for companies reporting serious adverse events for IND-exempt bioavailability/bioequivalence studies

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RECENT POLICY INITIATIVES

- The draft guidance incorporates concepts pertaining to investigator responsibilities for adverse event reporting described in the guidance for industry and investigators entitled “Safety Reporting Requirements for INDs and BA/BE Studies” (December 2012)
- It also incorporates concepts from the guidance for clinical investigators, sponsors, and IRBs entitled “Adverse Event Reporting to IRBs—Improving Human Subject Protection” (January 2009)
- When finalized, this guidance will supersede the 2012 and 2009 guidances.

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RECENT POLICY INITIATIVES

- FDA issued a draft guidance document entitled “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials: Guidance for Industry"
- It issued in April 2022
- The guidance’s purpose is to provide recommendations to sponsors developing medical products on the approach for developing a Race and Ethnicity Diversity Plan to enroll representative numbers of clinical trial participants from underrepresented racial and ethnic populations in the United States.

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RECENT POLICY INITIATIVES

- These racial and ethnic groups include Black or African American, Hispanic/Latino, Indigenous and Native American, Asian, Native Hawaiian and other Pacific Islanders, and other persons of color.
- Individuals from these populations are frequently underrepresented in biomedical research despite having a disproportionate disease burden for certain diseases relative to their proportional representation in the general population.

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RECENT POLICY INITIATIVES

- Per FDA, adequate representation of these populations in clinical trials and studies supporting regulatory submissions helps ensure that the data generated in the development program reflect the racial and ethnic diversity of the population expected to use the medical product if approved
- It potentially also may identify effects on safety or efficacy outcomes that may be associated with, or occur more frequently within, these populations, according to FDA.
- The guidance focuses specifically on racial and ethnic demographic characteristics of study populations, recognizing the broader issues regarding health disparities and differential access to health care in certain racial and ethnic populations.

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RECENT POLICY INITIATIVES

- In the draft guidance, FDA advises sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, including other underrepresented populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity.
- FDA also encourages sponsors to submit plans that help ensure the adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant subpopulations.

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RECENT POLICY INITIATIVES

- This guidance expands on FDA's guidance, "Collection of Race and Ethnicity Data in Clinical Trials (October 2016), which outlines how to collect and present race and ethnicity data in submissions to the FDA and recommends that sponsors develop and submit a plan to address inclusion of clinically relevant populations, for discussion to the Agency.
- Given the importance of increasing enrollment from historically underrepresented racial and ethnic populations, FDA published this guidance to provide detail on what sponsors should include in a Race and Ethnicity Diversity Plan.

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RECENT POLICY INITIATIVES

- FDA recommends that a Plan to enroll representative numbers of participants from historically underrepresented racial and ethnic populations be submitted to the Investigational New Drug (IND) application for a drug or biological product, or the Investigational Device Exemptions (IDE) application for a device.
- This Plan should be discussed with the FDA as soon as practicable during medical product development.

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RECENT POLICY INITIATIVES

- FDA issued a guidance document entitled "Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank: Guidance for Responsible Parties, Submitters of Certain Applications and Submissions to FDA, and FDA Staff"
- It issued in August 2020
- This guidance document is intended to describe the current thinking of FDA CDER, CBER and CDRH regarding civil money penalties under Section 303(f)(3) of the FDC Act.

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RECENT POLICY INITIATIVES

- That section authorizes FDA to assess civil money penalties against
  - Responsible parties and/or submitters of certain applications and submissions to FDA
  - For drug products, biological products, and device products
  - Who violate applicable FDC Act prohibitions relating to requirements under Section 402(j) of the Public Health Service Act (PHS Act),including its implementing regulations in 42 CFR part 11, to submit clinical trial registration and/or results information to the ClinicalTrials.gov data bank and/or certain certifications to FDA.

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RECENT POLICY INITIATIVES

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- The guidance document addresses the following questions:
- How do the Centers intend to identify whether responsible parties have failed to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank or submitted false or misleading information to the data bank, or whether submitters have failed to submit to FDA the certification required by Section 402(j)(5)(B) of the PHS or knowingly submitted a false certification to FDA?
- Under what circumstances may a Center decide to seek civil money penalties against a responsible party or submitter?

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RECENT POLICY INITIATIVES

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- What procedures apply when a Center seeks civil money penalties?
- What civil money penalty amounts may be assessed for:
  - Failing to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank
  - Submitting false or misleading information to the data bank
  - Failing to submit the required certification to FDA
  - Knowingly submitting a false certification to FDA?

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- Combatting fraud in clinical trials continues to be a major focus for the government.
- Examples of fraudulent activity include:
- Making materially false representations about clinical trials.
- Fabricating data on the participation of subjects in clinical trials

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- Concealing from FDA, sponsors and contract research organizations the fact that the data and participation of subjects had been fabricated
- Some case studies of note include the following matters on the subsequent slides

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- See 86 Fed. Reg. 41483 (August 2, 2021)
- FDA issued one year debarment order
- FDA found that a Research Manager and others conspired to cause the introduction of misbranded and adulterated drugs into interstate commerce with the intent to defraud and mislead the US by manipulation and falsification of test data and information;

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- See also 87 Fed. Reg. 14539 (March 15, 2022), 87 Fed. Reg. 23184 (April 19, 2022) and 86 Fed. Reg. 66566 (November 23, 2021)
- FDA issued permanent debarment orders
- Study coordinators/receptionists fabricating medical records to portray persons as legitimate study subjects when they were not. Additional violations included falsifying records to make it appear that the study subjects had consented to participating in the study, satisfied the study's eligibility criteria, appeared for scheduled visits at the study's site, taken study drugs as required, and received checks as payment for site visits.

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- FDA issued five year debarment order for the following.
- Clinical research coordinator's falsification of case report forms—regarding volunteers' participation in the study and performance of the study drug.
- FDA found that, had the sponsor submitted a new drug application containing the falsified data, FDA may have relied on the fabricated information to approve a new drug product, and such reliance could have compromised public health.

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- Various recent Warning Letters have issued for the following alleged violations:
- Not having IRB approval
- Lacking documented informed consent obtained from each subject
- Failure to maintain adequate records of each subject's exposure to the investigational device and outcomes in accordance with the investigational plan.

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

- No source documents available at clinical site
- Concerns with validity and integrity of data collected at the site
- Failure to ensure proper monitoring
- Failure to submit complete and accurate progress reports

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RECENT CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

- Failure to maintain accurate, complete and current records of shipment, receipt, use, or disposition of a device
- Failure to maintain the records during the investigation and for a period of 2 years after the date on which the investigation is terminated or completed.
- Failure of study director/quality assurance unit to fulfill regulatory responsibilities

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RECENT NON-CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- An interesting recent trend is FDA addressing violations of Good Laboratory Practice for Nonclinical Laboratory Studies
- Violations included:
- Failure to conduct nonclinical laboratory studies in accord with protocols
- Failure of quality assurance unit to inspect each nonclinical laboratory study at intervals adequate to assure the study's integrity

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RECENT NON-CLINICAL VIOLATIONS TRIGGERING COMPLIANCE ACTIONS

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- Failure to maintain written and properly signed records
- Failure to document in writing the responsibilities and procedures of the quality assurance unit
- Failure to ensure that specimens are properly identified by test system, study, nature and date of collection
- Failure to ensure that the testing facility maintains a current summary of training and experience for each individual engaged in or supervising the conduct of a nonclinical laboratory study.

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AVOIDING REGULATORY PROBLEMS

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- What should you do to meet FDA expectations and avoid regulatory problems in clinical and non-clinical research?
- The answer is multifaceted
- There are many important steps to achieve and maintain substantial compliance.

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AVOIDING REGULATORY PROBLEMS

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- Take the time to read and understand the relevant statutory provisions, regulations and FDA guidance documents
- Hire regulatory professionals who are knowledgeable in the subject matter area
- Create standard operating procedures with processes and controls which ensure substantial compliance

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AVOIDING REGULATORY PROBLEMS

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- Train your employees on the law, FDA policy and your standard operating procedures
- When in doubt, utilize expert outside assistance
- If there is still a question, do not be afraid to engage FDA on an issue

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Thank You!

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