Mini Summit XIV: Clinical Trial Disclosure and Results Reporting Liability under FDAAA, Section 801

Jarilyn Dupont, JD
Director of Regulatory Policy, Office of Policy
Office of Commissioner, U.S. Food and Drug Administration

Ann Meeker O'Connell, MS, CCEP
Acting Division Director, Good Clinical Practice Compliance,
Office of Scientific Investigations, Office of Compliance
Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

General Statutory Responsibilities Related to ClinicalTrials.gov Data Bank

- Submission of clinical trial information required under section 402(j) of the Public Health Service Act (42 U.S.C. § 282(j))
  - includes registration of applicable clinical trials (as statutorily defined)
  - periodic updates
  - for approved products – submission of results information
- Submission of certification form, Form FDA 3674 (Certification of Compliance), to FDA to accompany certain applications
- Inclusion of mandatory statement concerning ClinicalTrials.gov in informed consent documents and processes (21 C.F.R. § 50.25(c))
- Annual Grant Reports – certify compliance with requirements

FDA's Specific Responsibilities

- **FDA's Compliance/Enforcement and Other Responsibilities**
  - Compliance/Enforcement of Registration/Results submission requirements under 402(j) Public Health Service Act (21 USC 282(j))
  - Form FDA 3674 (Certification of Compliance with ClinicalTrials.gov requirements) submitted to FDA
  - FDA Grants – additional oversight of grantees - Orphan Grants program determines that the clinical trials funded are registered with ClinicalTrials.gov and annual reports contain additional assurances
  - Informed Consent Regulation (21 C.F.R. § 50.25(c))

FDA's Specific Responsibilities

- Periodic Reports on Postmarketing Requirements – section 505(o)(3)(E) of the FD&C Act
- Notification to NLM/NIH of certain FDA regulatory actions on marketing applications – FDA notifies NLM/NIH of product approvals
- Linking of FDA health product information to specific ClinicalTrials.gov NCT record – advisory committee meetings, pediatric assessments, public health advisories, approval packages, labeling

Certification of Compliance – Form FDA 3674

- Submission Issues
  - Failure to submit Form FDA 3674 with application
    - "Acknowledgement" letter – paragraph is included in the letter acknowledging application submissions, identifying the failure to submit the form.
  - Certain companies are not following the FDA guidance on when the FDA 3674 should be submitted and with which submissions. Guidance is at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm
    - One company submitted about 50-60 forms – submitted with every single filing with FDA, including correspondence – which is unnecessary

Certification of Compliance – Form FDA 3674

- Forms being reviewed for use in actions to be taken by agency
- In 2011, CDER alone received approximately 6,000 forms
- Clinical Trials Information Processing System (CTIPS)
  - IT system designed to extract information, particularly NCT#s, from the Forms FDA 3674 and match to marketing applications
  - Information maintained in the CTIPS system to match approvals to health and safety information necessary for the required linking to the ClinicalTrials.gov data bank by NCT# and the notification to NIH of actions taken by FDA
  - Information in CTIPS designed to eventually be used in other agency compliance/enforcement activities

Other FDA Actions

- Informed Consent - 21 C.F.R. § 50.25(c) - FDA has the authority to regulate the protection of human subjects and the authority impose penalties for violations of these regulations. The FD&C Act prohibits failing to maintain records or make reports required under section 505(i) and failing or refusing to comply with requirements under section 520(g)

- Check ClinicalTrials.gov records against IND/IDE records

- Use Form FDA 3674 and ClinicalTrials.gov submissions to prepare audit/inspection data

Other FDA Actions

- March 11, 2011: Revised Compliance Program Guidance Manual (CPGM) CP 7348.810, Sponsors, Contract Research Organizations, and Monitors
- Includes section on "Registration of Studies on ClinicalTrials.gov"
  - Evaluation of sponsor compliance with SOPs (if any) for complying with the requirements associated with *ClinicalTrials.gov*
  - Determination of whether the trial(s) being inspected was/were registered on *ClinicalTrials.gov*, if required
  - For registered trials:
    - assessment of timing of registration vs. date first subject enrolled;
    - determination of whether primary and secondary outcome measures are captured in *ClinicalTrials.gov* and are generally accurate
  - Evaluation of compliance with 21 CFR Part 50.25(c)

Other Government Actions

- Under the Health Care Fraud and Abuse Control Program (HCFAC), FDA receives funds to detect, prosecute, and prevent pharmaceutical, biologic, and medical device fraud.
- FDA gathers information from sources inside and outside the Agency on suspected fraudulent marketing schemes, application fraud, clinical trial fraud, and flagrant manufacturing-related violations related to drugs, biologics, and medical devices.
- Representative cases include the following:
  - marketing of drugs for uses not approved by FDA
  - failing to report safety information to FDA concerning defective medical devices
  - falsifying records in the conduct of clinical trials, including forging signatures of clinical investigators, enrolling ineligible subjects, and providing false information to FDA

Prayle et al Publication on Results Reporting on ClinicalTrials.gov

BMJ

BMJ 2011;344:d7373 doi: 10.1136/bmj.d7373 (Published 3 January 2012)

RESEARCH

Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study

OPEN ACCESS

Andrew P Prayle *NIHR doctoral research fellow*, Matthew N Hurley *Wellcome Trust paediatric clinical research fellow*, Alan R Smyth *professor of child health*

- Evaluated whether trial results were present on ClinicalTrials.gov for records that the authors deemed to require results reporting under FDAAA
- Reported that only 22% of these trials had reported results within one year of completion of the trial.

Prayle et al Methodology

- Authors deemed trials were subject to FDAAA if they were:
  - Interventional trials of a drug, device, or biological agent
  - Had at least one US site
  - Registered as phase II or later
- Authors deemed results overdue for a trial if:
  - Investigated a drug that already had approval from the Food and Drug Administration
  - > 1 year elapsed from trial completion date
  - Results were not available on ClinicalTrials.gov website

Number of ClinicalTrials.gov Records in Prayle Dataset By Type	
Interventional Trials	83, 579
With Recruitment Status of "Completed"	31, 556
With Completion Date 01 Jan – 31 Dec 2009	5,642
Deemed "Covered by the FDAAA"	1465
Studying an FDA-approved drug (per Drugs@FDA)	738
Results Present	163

Representative Limitations of Prayle Analysis

- Did not account for all elements of statutory definition for "applicable clinical trial" of a drug, e.g.
  - Controlled
  - Clinical Investigation as defined by 21 CFR 312.3

- May have included unapproved products
  - Manufacturer A has approval for Drug X
  - Manufacturer B has approval for Drug Y
  - Applicant C is seeking approval for a fixed-dose combination of Drugs X and Y
  - FDA would generally consider the fixed-dose combination to be a new drug.

- Results may have been timely submitted but were in quality review by NLM prior to posting

FDA Preliminary Review of Prayle Results

Source	Results posted	Results submitted but in quality review	Results Not Required and Not Submitted	Results Appear Overdue	Trial evaluating device not drug
Prayle et al	22.1%	Did not assess	Did not fully assess	77.9%	None noted
FDA Review: Results Not Submitted (As of Prayle Data Pull in January 2011)	22.1%	6.4%	36.6%	34.6%	0.4%
FDA Review: Results as of 31 May 2012	42.5%	4.9%	31.0%	21.1%	0.4%

Particular Issues to Consider

- **Industry Sponsors and Sponsor- Investigators Need To Consider:**
  - Standard Operating Procedures (SOP)
    - Are SOPs are current?
    - Do they reflect requirements to submit both registration **and** results information to ClinicalTrials.gov in a complete and timely manner?
  - Quality Control
    - Ensure that Form FDA 3674 matches ClinicalTrials.gov records
    - Journal Articles Published – Check that ClinicalTrials.gov records are updated
  - Responsible Parties
    - May want to ensure that relationship between investigator and company is clearly and specifically defined so that it is clear who is the “responsible party” based on the statutory provision