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Clinical Trial Registries and Results Databases: Recent Developments and the Impact of FDAAA

CBI Webinar

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Overview

- Underlying Policy Considerations
- Developments from FDAMA to FDAAA
- FDAAA Requirements and Implementation Timelines
- Open Issues and Challenges

Policy Considerations

- Facilitating access to clinical trials
- Accelerating clinical trial enrollment
- Addressing publication bias
- Disseminating research findings
- Ethical dimension

Developments

- FDAMA § 113 (1997)
- Establishment of clinicaltrials.gov (2000)
- Major changes in 2004
  - Pediatric data controversy involving SSRIs
  - New York AG lawsuits
  - AMA endorsement of comprehensive registry
  - PhRMA clinical trials principles
  - ICMJE policy

Developments

- 2005-2006
  - WHO minimal registration data set created
  - Maine registry and results law enacted
  - State and federal legislative proposals
  - Voluntary company initiatives
- 2007
  - Revised ICMJE policy (June)
  - FDA Amendments Act (FDAAA) (September)

Developments - Revised ICMJE Policy

"The ICMJE recognizes the potential benefit of having information about preliminary trials in the public domain, because these studies can guide future research or signal safety concerns."

Laine et al., Clinical Trial Registration: Looking Back and Moving Ahead, JAMA Online (June 4, 2007)

FDAAA – Expanded Scope of Registry

- Drugs → all non-phase 1 clinical trials
- Devices → all controlled clinical trials (except feasibility)
- Devices → pediatric postmarket surveillance studies

FDAAA – Who Is the "Responsible Party"?

- Study sponsor, or
- Principal investigator, if so designated by a sponsor
- If the PI is the responsible party, must have
  - Access to and control over the data
  - Right to publish the trial results
  - Ability to meet all submission requirements

FDAAA – What Must Be Submitted?

- Descriptive information
  - Brief title intended for lay public
  - Brief summary intended for lay public
  - Primary purpose
  - Study design
  - Study phase (for drug trials)
  - Study type
  - Primary disease or condition being studied
  - Intervention name and type
  - Study start date
  - Expected completion date
  - Target number of subjects
  - Outcomes, including primary and secondary measures

FDAAA – What Must Be Submitted?

- Recruitment information
  - Eligibility criteria
  - Gender
  - Age limits
  - Whether trial accepts healthy volunteers
  - Overall recruitment status
  - Individual site status
  - Whether or not there is expanded access for those who don't qualify (drug trials only)

FDAAA – What Must Be Submitted?

- Location and contact information
  - Name of sponsor
  - Responsible party
  - Facility name and contact information
- Administrative data (made public "as necessary")
  - Unique protocol identification number
  - Other protocol identification numbers, if any
  - FDA IND/IDE number and the record verification date
- Any other information NIH requires "by regulation"

FDAAA – When Is Study Registration Due?

- By the later of …
  - 12/26/07, ongoing/new studies of serious conditions
  - 9/27/08, ongoing/new studies of non-serious conditions, or
  - 21 days after the first patient is enrolled
    - For serious conditions, studies beginning after 12/5/07
    - For non-serious, studies beginning after 9/6/08

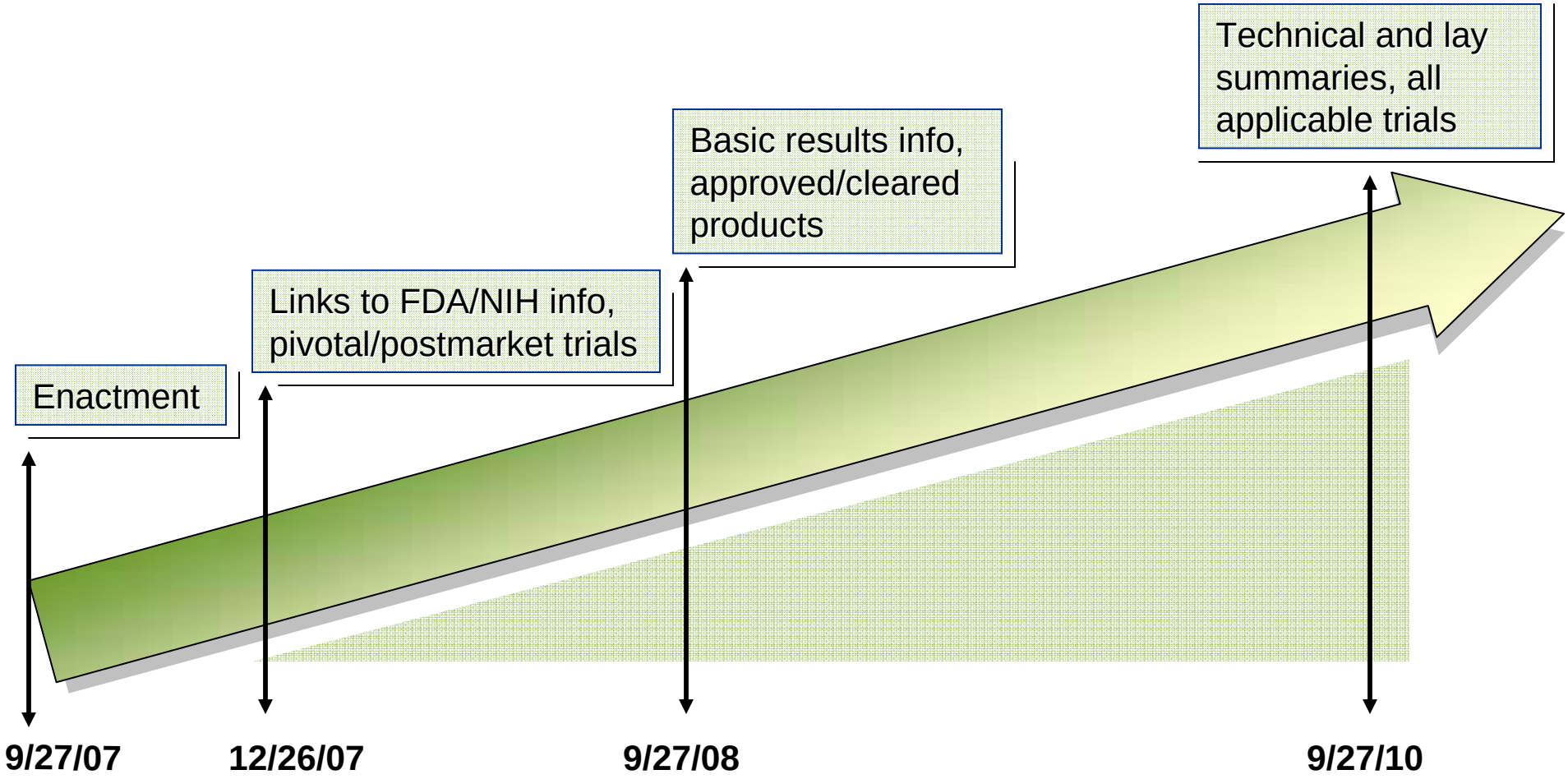
FDAAA – When Will NIH Post the Information?

- Drugs → within 30 days of submission
- Unapproved/cleared devices → not before, but no later than 30 days after, clearance or approval
- Approved/cleared devices → no later than 10/27/08

FDAAA – Registry Search Categories

- Keywords
- Categories
  - Disease or condition
  - Drug or device name
  - Location
  - Age group studies, including “pediatric subpopulations”
  - Study phase
  - Sponsor
  - Recruitment status
  - National Clinical Trial number or other study identifier
  - Safety issue being studied, if any (by 3/27/09)

FDAAA – Results Data Bank



FDAAA – Results Data Bank Phase 1

- Links to FDA/NIH information (beginning 12/26/07)
- Applies to pivotal trials or postmarketing studies only
- No data submission required
- Timing of posting by NIH
  - Not earlier than 30 days after approval/clearance, or
  - Not later than 30 days after the information becomes public
- NIH may include entries for trials submitted to the data bank prior to FDAAA

FDAAA – Results Data Bank Phase 1

- Mandatory information
  - FDA advisory committee summaries
  - Pediatric results assessments
  - FDA public health advisories
  - Summary basis for approval (drugs)
  - PMA or 510(k) summaries (devices)
  - NIH Medline citations
  - National Library of Medicine structured product labeling (if any)

FDAAA – Results Data Bank Phase 2

- Basic results for applicable trials of approved or cleared products (by 9/27/08)
  - Demographic and baseline characteristics
  - Primary and secondary outcomes measures
  - Point of contact
  - Agreements restricting principal investigators' ability to present or publish results

FDAAA – Results Data Bank Phase 3

- Expansion by HHS regulations (by 9/27/10)
- Required elements
  - Full protocol or information needed to evaluate results
  - Technical summary, if feasible
  - Lay summary, if feasible
- Feasibility requires summaries to be
  - Non-promotional
  - Non-misleading

FDAAA – Results Data Bank Phase 3

- Regulations must establish
  - Standard submission format
  - Whether to use WHO data elements set
  - Timing and rules for updating clinical trial information
  - Quality control/verification procedures
  - Whether to include expanded results information for trials of unapproved products and submission timing (taking delayed submission certification process into account)

FDAAA – Submission of Results Information

- Within 1 year of estimated or actual completion date
- Delayed submission of results with certification
  - For new approvals, 30 days after approval
  - For new uses, within 30 days of FDA decision
  - Maximum period of 2 years after certification
- Extensions for good cause
- Waivers for extraordinary circumstances
- NIH to post information within 30 days

FDAAA – Adverse Event Information

- By 3/27/09, FDA must issue regulations on including serious and frequent drug (and device) AE information in the data bank
- If no regulations issued, default rule requires
  - Table of SAEs grouped by organ system
  - Table of non-serious AEs with frequency > 5% in clinical trials, by organ system

FDAAA – Updating Requirements

- Responsible party must update information (including outcomes) at least annually
- Updates within 30 days required for
  - Recruitment status changes
  - Study completion

FDAAA – Enforcement Provisions

- Grant forms for government-funded studies must certify compliance
- Certification required in any NDA, BLA, PMA, or 510(k)
- Quality control
  - 3-year pilot project on verifying accuracy of information in data bank
  - Notice and 30-day opportunity to remedy any inaccurate, false, or misleading information submitted to data bank

FDAAA – Enforcement Provisions

- Public notice of violations
  - "The entry for this clinical trial was not complete at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry."
  - "The entry for this clinical trial did not contain information on the primary and secondary outcomes at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry."
  - "The entry for this clinical trial was found to be false or misleading and therefore not in compliance with law."
- NIH must make the data bank searchable for such compliance entries

FDAAA – Enforcement Provisions

- New prohibited acts (FDCA § 301)
  - Failure to submit required clinical trial information
  - Submission of false or misleading clinical trial information
  - Failing to certify or knowingly submitting a false certification in an NDA, BLA, PMA, or 510(k)
- Civil money penalties
  - Up to $10,000 for all violations adjudicated in a single proceeding, plus
  - If not corrected within 30 days of notice, $10,000 per late day

FDAAA – Other

- Upon expansion to the full results data bank (3 years), state and local registration or results database requirements are preempted
- Rule of construction provides that submitting information on off-label trials is not evidence of off-label promotion
- Within 12 months, FDA shall issue guidance on how the data base provisions apply to a pediatric postmarket surveillance that is not a clinical trial

Open Issues and Challenges

- Effect of ICMJE policy on publication of phase 1 studies?
- NIH “required” elements for trial registration?
- Will there continue to be a role for company websites?
- Increased pressure to provide expanded access?
- Effect on sponsor-investigator agreements?
- Effect on “seeding” studies?
- Effect on investigator-initiated studies?
- Effect of greater transparency on product liability?

Questions?

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