Federal Legislation for Clinical Trial Registration and Results Disclosure: A New Era in Publication Planning

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Presentation Agenda

Background:
- Clinical Trial Registration – Then and Now

Review Pending Legislation
- Changes for Registration
- Trial Results Disclosure – What, When, How
- Status of Bills
- Implications…

Questions & Discussion
Background: PDUFA

- **PDUFA 1992**
  - Allowed FDA funding by industry to support additional staff/resources for review of NDAs
  - Goal: increase timeliness and *predictability* of review actions, while maintaining quality

- Generally regarded as successful, though some criticisms of COI at agency
1997 PDUFA Reauthorized

- Part of FDAMA (FDA Modernization Act)
- Section 113: Included provisional requirement for clinical trial registration on [NIH] public website (www.clinicaltrials.gov)
  - Required only for efficacy trials for “serious and life-threatening conditions”
  - Did not address trial results disclosure
  - CT.gov activated in 2000 – initial response slow

2002 PDUFA Reauthorized & MDUFMA passed

- no change for trial registration
Clinical Trial Registration: ICMJE

**2004**
- ICMJE mandates trial registration at study initiation, on a publicly accessible website, as a condition for [possible] subsequent publication
- Intense discussions of dataset requirements

**2005**
- Policy finalized – specifies “clinically directive” trials must be registered at inception; ICTRP format
- > 600 medical journals adopt policy
- Policy is SILENT re: trial results disclosure
Industry –

• PhRMA/IFPMA/EFPIA/JPMA publish position statements on trial registration and commit to publicly disclose results of trials [of marketed products] within 12 mos of study completion, but not to prevent peer-reviewed publication

• PhRMA establishes www.clinicalstudyresults.org

• Several companies do same – use ICH E3 summaries

State of Maine

• Enacts legislation 2006-7 requiring trial registration per ICMJE policy, and public disclosure of study results within 12 (24) mos of completion
Caught Between a Rock and a Hard Place…

• Several companies* have manuscripts for peer-reviewed publication rejected by journal editors due to “prior publication” – i.e., they have posted summaries on company websites or on CSR.org, per industry position (and Maine legislation)

ISMPP Annual meeting, April 25-26, 2007.
Major Policy Changes

- ALL human interventional studies must be registered at study inception (aligns with WHO)
  - Include phase 1 PK / toxicology / device feasibility trials

Trial Results Disclosure Addressed

- “For the present, the ICMJE will not consider results posted in the same primary clinical trials register in which the initial registration resides as previous publication if the results are presented in the form of a brief, structured (< 500 words) abstract or table.”
- “...parties ... should consider [posting] such an abstract in the registry 24 months after closure of data collection if results are not published in a peer-reviewed venue by that time.”
- “Researchers should be aware that editors may consider more detailed deposition of trial results in publicly available registries to be prior publication.”
Similar bills passed by House and Senate

• Include legal requirements for registering clinical trials and disclosing results with specified deadlines
  – Significant penalties for failure to comply
• Both bills pre-empt and supersede any state laws
• House bill: more prescriptive
• Reconciliation conference will take place in Sept.
  – House bill expected to take precedence

PDUFA/MDUFMA 2007 (FDARA)
House and Senate Bills: “Applicable Trials”

**House**
- Any clinical trial conducted to test safety or effectiveness of a drug or device, whether federally or privately funded...includes studies ex-US if part of an application...
- Excludes phase 1 unless testing PK in a special population
- Excludes small clinical trials of device feasibility or of device prototypes
- FDA must decide whether to expand CT.gov, or “supplant” it

**Senate**
- **Drugs**: Any controlled clinical investigation other than a phase 1 study
- **Devices**: A prospective study of health outcomes comparing the intervention against a control in human subjects...to support an application, other than a limited study to...refine the device or design a pivotal trial

Content: both specify ICTRP registration data set
House and Senate Bills: Registration Timing

**House**
- NIH Director must establish registry database no later than 1 year after enactment
- Sponsor must register ≤ 14 days after FPI and update q 6 mos

**Senate**
- Regulations to be set 18 mos after enactment and become effective 90 days after issuing final rule
- Sponsor must register ≤ 21 days after FPI
- Drug trial registrations will be posted publicly ≤ 30 days of submission
  Device trial registrations will be posted publicly ≤ 30 days of FDA clearance or approval
House and Senate Bills: Results Database

**House**
- **Scope**: Must contain all applicable clinical trials, as defined for registration
- NIH Director must establish by 1 yr after enactment and administer
- Searchable by public - terms include indication(s); whether an application is pending, submitted, approved or withdrawn; drug name; phase of trial; sponsor.
- Calls for publication of a summary of FDA medical and clin pharm reviews ≤ 90 days after FDA action

**Senate**
- **Scope**: Must include links to results information for clinical trials that form the 1º basis of an efficacy claim and for post-approval or post-clearance clinical trials
- NRM (Negotiated Rule Making process) to determine how to ensure quality/validity of info., and timing of results posting – may take up to 30 mos
- Calls for feasibility study to find best way to make trial results publicly available, by 18 mos _NLM meeting July 16-17_
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| **Content:** A “non-promotional” lay summary in non-technical terms understandable to patients – including any changes to trial design post-registration, and any significant safety information. A “non-promotional” technical report, including data on percent of subjects who discont’d (and why). | **Content:** Results information first comes from existing FDA and NIH documents and peer-reviewed publications. Heavy reliance on FDA reviews, Advisory Committee backgrounds and any FDA public health advisories.  
- **Drugs:** SBOA  
- **Devices:** SSE |
| Sponsor must provide information on any agreement with any non-employee that restricts ability of that person to discuss, present, or publish results of the trial… | |

Both: links to any Medline citations of a trial and to the entry for the drug in the NLM database of structured product labels
House and Senate Bills: Results Database

**House**

- **Timing:** Clinical trial results information must be submitted no later than 1 year after the *earlier* [sic] of a) estimated trial completion date or b) the actual completion date.
  
- Delays are possible “for good cause” or if seeking peer-reviewed pub.
  
- Updates to results submitted *must be provided q 6 mos X 10 years*
  
- **Public Disclosure:** For pre-approval studies, 30 days after drug or device approved or cleared, or FDA sends a Not Approvable or NSE letter. For post-approval studies, 30 days after submission. Some delays possible

**Senate**

- **Timing:** Links to results of included trials in data bank not earlier than 30 days after FDA approval or clearance of drug or device; or not later than 30 days after such information becomes publicly available
  
- **Public Disclosure:** Results become public only after FDA approval or clearance, or after they otherwise become publicly available

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*House and Senate Bills: Results Database*
NLM invited stakeholders to provide advice on design of a Public Results Database Feasibility Study.

- Meeting co-chaired by D. Zarin (CT.gov) and R. Califf (Duke)
- Attendees included many from NLM, NIH, FDA; CMS, Consumers Union; patient advocates; several state AGs; academics; 2 ICMJE editors; 2 industry reps

NLM considering 2 possible formats –

- A structured abstract following CONSORT – mostly text
- A summary using the ICH E3 format - mostly tabular

F. Rockhold presented the GSK experience

- ~ 3,000 summaries posted in its trial results database
Questions put to the attendees:

a. types of users of the results databases, and an evaluation of the degree to which different formats might meet their needs
b. methods for evaluating these database formats and what parameters could demonstrate their utility
c. resource implications and feasibility of the two formats
d. possibilities that unintended negative consequences could arise from the use of a database entry due to misunderstandings or the inability to consider trial design, other research or other treatment options when interpreting trial results
e. other questions that should be addressed by the feasibility study.
No agreement or consensus reached

Attendees did not identify who the primary audience is (or will be) for a results database

NIH/NLM is preparing for legislation enactment – and prefers a feasibility study will be specified

NLM is concerned about House provisions for a “non-technical summary,” as well as technical summaries that are not peer-reviewed

Posting of raw data also discussed – AGs and C.U. favorably disposed. Most others were not
House and Senate Bills: Enforcement Common Provisions

- Prohibit release of federal research grant funds to any person not compliant with FDARA regs – starting 210 days post enactment
- FDA must verify compliance when considering an IND/IDE; may impose a clinical hold if the trial wasn’t registered
- FDA must verify compliance prior to filing an NDA, 510(k), or PMA and if not remedied ≤ 30 days, must refuse to file the application
- Failure to submit required clinical trial info, and submission of info that is “promotional,” false or misleading are deemed prohibited acts under the FDCA _ civil penalties
  - Senate: $10,000 for 1st violation, $20,000 for subsequent ones
  - House: if not corrected ≤ 30 days, not more than $15,000 for an individual or non-profit entity in a single proceeding; and $10,000/day for others
Key Issues and Questions

Logistical

• Posting others’ data is not NIH’s mission

• How to know if public disclosure of trial results is “successful”? Efficient? “Optimal”? Etc.

• Who will compose summaries that are not from the FDA or the peer-reviewed literature?

How to protect against “bias”?

• Legislation specifies penalties for “promotional” postings…

• Legislation does not stipulate posting of the study protocol – Bob Temple has advocated this to prevent data “diddling”
Key Issues and Questions

Implications for Industry Sponsors

- This is a major intrusion of government into clinical research and its publication
- Public registration is not new; results disclosure within specific timeframes (by law) is
- Will there be loss of IP and of trade secrets? Generic applications may be encouraged/facilitated
- Will the ROI be better for a ‘fast follower’ than an originator?
- How will this all affect peer-reviewed journals?
- How will this affect day-to-day publication planning and development?
Key Issues and Questions

Potential [Unintended] Consequences

- Data dredging and statistical associations...
- Results databases are not substitutes for active post-marketing surveillance
- Possible pressures by patients on physicians to modify prescribing based on public postings, not peer-reviewed
- Medical malpractice litigation? Product liability actions?
- Formulary decisions? Insurance reimbursements?
- Investor reactions… 1st study positive, second isn’t…?
- Administrative resources for sponsors???
Fisher, C. Clinical Trials Results Database: Unanswered Questions. *Science* 2006; 311; 180-181*


Trial registry bill should request protocol with results, FDA’s Temple says. *The Pink Sheet* 2007; 69: 29; 20

Senate Bill S.1082*

House Bill HR 2900*

Comparison of House and Senate Provisions for Clinical Trials Registry and Results Databases*

- Prepared by PhRMA, this chart reflects H.R. 2900 as reported from House Energy & Commerce Committee on June 28, 2007, and the version of S. 1082 as passed by the Senate on May 9, 2007

*Available at www.ISMPP.org*
Update on PDUFA 2007: Potential Impact on Publication of Clinical Trials’ Data

Questions & Discussion