Clinical Trials Disclosure

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Outline

• Rationale for clinical trial registration and results reporting
• Key policies and laws
• Implications of non-compliance with clinical trial disclosure requirements (ClinicalTrials.gov)
• Yale University status of registration and reporting
• ICMJE and clinical trial disclosure
• Grant requirements
• Finding help at Yale
By KENNETH N. GILPIN

The New York State attorney general accused the British drug giant GlaxoSmithKline of consumer fraud today, asserting that the company had withheld negative information and misrepresented data about the efficacy and safety of prescribing the antidepressant drug Paxil to children.

The civil lawsuit, filed in New York State Supreme Court, says that starting in 1998, Glaxo suppressed the results of four studies that did not find the drug effective in treating children and adolescents and that suggested a possible increased risk of suicidal thinking and acts.

"By concealing critically important scientific studies on Paxil, GlaxoSmithKline impaired doctors' ability to make the appropriate prescribing decision for their patients and may have jeopardized their health and safety," the attorney general, Eliot Spitzer, said in a statement.
Incomplete Results

Kaplan-Meier estimates for ulcer complications according to traditional definition. Results are truncated after 12 months, no ulcer complications occurred after this period. Adapted from Lu 2001.

Why Mandatory Disclosure?

• Not all trials are published
• Publications do not always include all pre-specified outcome measures
• Unacknowledged changes are made to the trial protocol that would affect the interpretation of the findings
  – e.g., changes to the pre-specified outcome measures
History of ClinicalTrials.gov

- FDAMA* 113 (1997) mandates registry
  - Investigational New Drug application (IND) trials for serious and life-threatening diseases or conditions
- ClinicalTrials.gov launched in February 2000
- Calls for increased transparency of clinical trials
- FDAAA† Section 801 (2007): Expands registry & adds results reporting requirements

* Food and Drug Administration Modernization Act of 1997
† Food and Drug Administration Amendments Act of 2007
Why Are We Here?

• Most AMCs do a good job of registering protocols, but fail to monitor when results are due.

• Most academic medical centers (AMCs) have not fulfilled the commitment to post clinical trial results.

- Examined compliance with FDAAA-mandated reporting of applicable clinical trial (ACT) results on ClinicalTrials.gov completed between 1 Jan. and 31 Dec. 09.
  - Completed trials with primary completion date in 2009 (n=5,642)
  - FDAAA-mandated trials of approved products (n=738)<sup>1,2</sup>
  - Results reported (n=163)
  - Results not reported (n=575)

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<td><strong>738</strong></td>
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<sup>1</sup>www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, <sup>2</sup> included Phase II-IV trials of drugs, devices, biologics.
High Profile Problem: U.S. Congress

• U.S. Congress has expressed concern because
  • “…researchers and pharmaceutical companies routinely fail to publish data from clinical drug trials in a timely fashion.”\(^1,2\)
  • NIH is responsible for maintaining the public database of trial results on clinicaltrials.gov and FDA is responsible for enforcing the statutory requirements
  • NIH is not “…adequately implementing the law requiring such reporting.”
  • FDA is not “…adequately enforcing the law requiring such reporting.”

• FDA asked if it has issued warning letters, imposed fines or initiated enforcement action

1. Letter to Commissioner of the Food and Drug Administration, Waxman, Markey and DeGette, February 14, 2012
2. Letter to Director of the NIH, Waxman, Markey and DeGette, February 14, 2012
ICMJE Consequences of Not Registering Trials

- BMJ has rejected 10-20 manuscripts/year for failing to register clinical trials, in line with ICMJE policy.¹
- To date (Nov 2011), NEJM has rejected 66 papers for registration issues (8 for lack of proper registration, 58 for late registration) and have not granted appeals.²
- Yale has had manuscripts rejected from NEJM for noncompliant protocol registration
- Hundreds of non-ICMJE journals follow ICMJE practices

¹Personal communication between Barbara Godlew and Pamela Miller, NEJM. 28 Nov 2011.
²Personal communication between Barbara Godlew and Trish Groves, BMJ. 28 Nov 2011.
2004 Editorial (and updates)*
  – Effective Sept 2005

Prospective registration (before study start) is required to be eligible for publication

Which trials?
  – Interventional studies
    • All phases
    • All intervention types
    • Drugs, surgical procedures, devices, behavioral treatments, process-of-care changes

When to register?
  – Prior to enrollment of first participant

Where to register?
  – ClinicalTrials.gov or WHO Primary registry

* [http://www.icmje.org](http://www.icmje.org)
† World Health Organization
• Federal fine for not registering or reporting trials: potential for $10,000/day fine.

• Withholding remaining or future grant funding or recovery of monies already allocated

• NIH will verify that each ACT for which the grantee is the responsible party has been registered in ClinicalTrials.gov
FDAAA Registration Requirements

• **Which Trials?** ("Applicable Clinical Trials"")
  – Interventional studies of drugs, biologics, and devices
  – *Not* phase 1 drug or *not* small feasibility device
  – US FDA jurisdiction (e.g., IND/IDE or US site)
  – Initiated on or after 9/27/07 or ongoing as of 12/26/07

• **When Must Trials be Registered?**
  – Register at trial initiation, but not later than 21 days after enrollment of the first participant

Challenges in Results Reporting
FDAAA REPORTING REQUIREMENTS: APPLICABLE CLINICAL TRIALS (ACTs)

- Phase II, III, and IV interventional trials in marketed products or for a new use/indication in drugs, biologics, or devices
- Conducted under an IND or investigational device exemption (IDE)
- With one or more sites in the US
- Compound manufactured in the US (or its territories)
- Conducted outside US, but within FDA jurisdiction
- Clinical investigation of a drug can be an applicable clinical trial (ACT) under FDAAA even if it does not require an IND (e.g., Phase IV investigator-initiated trial not looking at new use/indication)

- Trials that DO NOT require results reporting according to FDAAA
  - Phase I trials
  - Observational studies

Results Reporting and Publication

• Results must be reported on ClinicalTrials.gov within 1 year of primary completion date (not always same as end of trial)

• Deadlines for reporting to ClinicalTrials.gov are independent of publication status

• Reporting to ClinicalTrials.gov will not interfere with publication*

• ClinicalTrials.gov records are linked, via NCT number, to publications

Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer’s Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, Dr.P.H., John K. Hsiao, M.D., M. Saleem Ismail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S., J. Michael Ryan, M.D., T. Scott Stroup, M.D., David L. Sultzer, M.D., Daniel Weintraub, M.D., and Jeffrey A. Lieberman, M.D., for the CATIE-AD Study Group*

CONCLUSIONS

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer’s disease. (ClinicalTrials.gov number, NCT00015548)
Grant Application Requirements
Competing grants and non-competing progress reports

• For competing applications and non-competing progress reports of ACTs:
  • NCT number
  • Brief title as defined by ClinicalTrials.gov
  • Identity of the responsible party (Human Subjects Section of the research plan)
• If new proposal: Human Subjects Section of research plan should include statement that application includes an ACT requiring registration in ClinicalTrials.gov.
• Requirements apply to all grant applications submitted to NIH on or after January 25, 2008 with an ACT in the proposed project
• Requirements apply to all progress reports for grants with ACTs with budget start dates of April 1, 2008 or later
• Include a Certification of Compliance (FDA Form 3674)—link below
  www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf
Grant Requirements

Responsible Party Responsibilities

- Determine if competing application/funded grant supports an ACT.
- If grant supports an ACT, determine the responsible party.
- Responsible party must register the ACT no later than 21 days after enrolling the first subject (ICMJE requirements differ!).
- Responsible party must regularly update information in the ACT record.
- Responsible party must report ACT results not later than 1 year after the primary completion date.
- Costs of FDAAA compliance will be generally be allowable as direct charges to NIH supported grants. While it is expected that these costs will be covered by the funds provided with the grant, administrative supplements could also be considered.*

*http://grants.nih.gov/ClinicalTrials_fdaaa/faq.htm
How is Yale doing?

- 353 protocols registered on ClinicalTrials.gov
  - Assessment of Yale-supplied data identified 238 trials as likely to be ACTs
  - 76 ACTs trials registered
  - 162 ACTs that should be registered, working hard to complete

- 4 results postings
  - # of ACTs requiring results posting: still determining - surveys to faculty in question

- ~87 Yale registered protocols with “unknown” status
  - Working on this, surveys to faculty in question coming
  - Public view on ClinicalTrials.gov website will show “status = unknown” for records that have not been updated or verified in >2 years
What can you do

• Huron recommendation is a new policy

• When in doubt register before enrollment begins
  • OnCore will help, but still implementing

• Must have biostatistical support from day 1; add it to your grants

• FDAAA requires registrations be:
  • “Verified” at least every 12 months (update verification date)
  • Updated recruitment status within 30 days of recruitment status change
  • Updated trial status within 30 days of trial completion
Yale Resources

- **Yale internal team:**
  - Biostats: Peter Peduzzi, Jim Dziura, 2 TBN masters
  - YCCI: Tesheia Johnson, Henry Durivage, Thihan Padukkavidana, and registration support staff

- **Going back**
  - Start with the ~240. Most high profile to least. Registration and results.
  - ~87 unknown, figure out status with faculty help
  - ~500 need to be revisited
YCCI News

YCCI’s Winter 2012 Newsletter is Here »
The Winter 2012 edition of the YCCI newsletter is devoted to our education programs. It highlights the latest round of Junior Faculty Scholars, contains profiles of an Investigative Medicine Program and TL1 trainee, and has updates on collaborations and events.
Read More...

Yale asks community to help us discover cures for disease »
Yale University is launching a major effort to recruit thousands of volunteers to participate in clinical trials testing new medications for common conditions. Find out how you can help.

From the Director
Welcome to the website for the Yale Center for Clinical Investigation.
Read more...

Clinicaltrials.gov Training Session
Click here to view the presentation given on 1/10/12 regarding clinical trial registration and reporting guidelines.
Registering a Study on ClinicalTrials.gov

Instructions to register a Yale sponsored trial on ClinicalTrials.gov

The ClinicalTrials.gov Protocol Registration System (PRS) is a web-based tool developed for submitting clinical trials information to ClinicalTrials.gov. Records submitted through the PRS (http://register.clinicaltrials.gov) are available to the public at ClinicalTrials.gov. A guided tour of the PRS and account application information are available at http://prsinfo.clinicaltrials.gov/

PRS users enter information about their clinical trials, ensuring that the information is correct, readily understood by members of the public, and updated in a timely manner.

For clinical trial results to be considered for publication in journals that adhere to the International Committee of Medical Journal Editors (ICMJE) standards, the ICMJE has mandated that all clinical trials which begin recruiting on or after July 1, 2005 must be registered with a public registry before the enrollment of the first
Thank you