Update: ClinicalTrials.gov
Trial Registration and Results Reporting

Deborah A. Zarin, M.D.
National Library of Medicine, NIH
December 2010
Reasons to Register Clinical Trials and Report Results

• Human Subject Protections
  – Allows potential participants to find studies
  – Assists ethical review boards and others to determine appropriateness of studies being reviewed (e.g., harms, benefits, redundancy)
  – Promote fulfillment of ethical responsibility to human volunteers – research contributes to medical knowledge

• Research Integrity
  – Facilitates tracking of protocol changes
  – Increases transparency of research enterprise

• Evidence Based Medicine
  – Facilitates tracking of studies and outcome measures
  – Allows for more complete identification of relevant studies

• Allocation of Resources
  – Promotes more efficient allocation of resources
The good news: We have a lot of information

- 100,151 registered trials from 9,963 Sponsors
  - 45% US sites only
- 2,677 Results entries from 472 Sponsors
- Access to data about individual clinical trials
  - Powerful search tools
  - Users can identify and track trials and outcome measures
- Unique source of information about CRE
Content of ClinicalTrials.gov Records

• One record per trial
• Registration record
  – Submitted at trial initiation
  – Summarizes information from trial protocol
    – Condition
    – Interventions
    – Design, etc
  – Includes recruitment information (e.g., eligibility, locations)
• Results record
  – Submitted after trial completion
  – Summarizes trial results
    • Participant flow
    • Baseline characteristics
    • Outcome measures (including statistical analyses)
    • Adverse events
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.)

Secondary Source ID: ClinicalTrials.gov/NCT00015548
# 510(k) Premarket Notification

**Device Classification Name**: Lung Sound Monitor  
**510(k) Number**: K091732  
**Device Name**: VRLXP, MODEL XP  
DEEP BREEZE LTD  
2001 Pennsylvania Avenue Nw  
Suite 950  
Washington, DC 20006  
**Applicant**: Jeff Baetz  
**Regulation Number**: 870.1875  
**Classification Product Code**: OCR  
**Date Received**: 06/11/2009  
**Decision Date**: 03/04/2010  
**Decision**: Substantially Equivalent (SE)  
**Classification Advisory Committee**: Anesthesiology  
**Review Advisory Committee**: Anesthesiology  
**Statement/Summary/Purged Status**: Summary Only  
**Summary**:  
**Type**: Traditional  
**Clinical Trials**:
- NCT00473291
- NCT00495430
- NCT00506467
- NCT00542282
- NCT00672893  
**Reviewed By Third Party**: No  
**Expedited Review**: No
The bad news:
Somebody has to enter the data!
Legal and Other Requirements
FDAAA
Sec. 801 Expanded Clinical Trial Registry

• Enacted on September 27, 2007
• Requires Trial Registration (Dec 2007)
  – Phase II-IV drug and device trials for all diseases
  – Data elements: ClinicalTrials.gov + ~ WHO/ICMJE
• Requires Results Reporting (Sept 2008)
  – Trials of FDA-approved or cleared drugs and devices
  – “Basic” Results: Baseline Characteristics, Primary & Secondary Outcomes, Statistical Analyses
  – Adverse Events (Sept 2009)
  – “Expansion” of results by rulemaking (Sept 2010)
• Added enforcement provisions
Potential Enforcement Provisions

• Notices of non-compliance
• Civil monetary penalties (up to $10,000/day)
• Withholding of NIH grant funds
Key Terms

• Responsible Party
  – Sponsor, grantee
  – PI, if designated

• Applicable Clinical Trials
  – Interventional trials
  – Phase 2-4 drug, biologic, device
  – IND/IDE trial or ≥one site in U.S.
  – Ongoing as of 12/26/07, or later

• Primary Completion Date
Establishing the “Responsible Party”

• Who is the sponsor?
  – IND/IDE holder
  – NIH grantee
  – “Initiator of trial”

• Sponsor may designate the PI (under some conditions)

• RP has legal responsibilities for FDAAA
  – Others may help
  – Only one per trial!
Pitfalls in determining if your trial is an ACT

• Is it an interventional study?
  – Are the “interventions” a consequence of the research protocol, or vice versa?
  – Would the participants have received the interventions whether or not they were in the study?

• Does it include a device?
  – FDA regulatory definitions apply
  – Includes diagnostic devices
Lung cancer trial results show mortality benefit with low-dose CT:
Twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray.

The National Cancer Institute (NCI) is today releasing initial results from a large-scale test of screening methods to reduce deaths from lung cancer by detecting cancers at relatively early stages.

The National Lung Screening Trial (NLST), a randomized national trial involving more than 53,000 current and former heavy smokers ages 55 to 74, compared the effects of two screening procedures for lung cancer -- low-dose helical computed tomography (CT) and standard chest X-ray -- on lung cancer mortality and found 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT. The NLST was sponsored by NCI, a part of the National Institutes of Health, and conducted by the American College of Radiology Imaging Network (ACRIN) and the Lung Screening Study group. A paper describing the design and protocol of the NLST, “The National Lung Screening Trial: Overview and Study Design” by the NLST research team, was published yesterday by the journal Radiology and is openly available at http://radiology.rsna.org/cgi/content/abstract/radiol.10091808 .
National Lung Screening Trial (NLST)

This study is ongoing, but not recruiting participants.

First Received: October 3, 2002  Last Updated: June 15, 2010  History of Changes

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>National Cancer Institute (NCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborator</td>
<td>American College of Radiology Imaging Network</td>
</tr>
<tr>
<td>Information provided by:</td>
<td>National Cancer Institute (NCI)</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00047385</td>
</tr>
</tbody>
</table>

Purpose

RATIONALE: Screening tests may help doctors detect cancer cells early and plan more effective treatment for lung cancer. It is not yet known whether helical CT scan is more effective than chest x-ray in reducing death from lung cancer.

PURPOSE: Randomized clinical trial to compare the effectiveness of helical CT scan with that of chest x-ray in screening individuals who are at high risk for developing lung cancer.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>Procedure: bronchoscopic and lung imaging studies</td>
</tr>
<tr>
<td></td>
<td>Procedure: comparison of screening methods</td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Control: Active Control
Primary Purpose: Screening

Official Title: National Lung Screening Trial
Basic Results Database
Basic Results Reporting Requirements

• Results of FDA-approved/cleared products
• Generally, submission within 12 months of the earlier of estimated/actual primary completion date
• Delayed Submission of Results
  – Seeking initial approval
  – Seeking approval of a new use
  – Extensions for “good cause”
Basic Results Modules

- Participant Flow
- Baseline and Demographic Characteristics
- Outcome Measures
- Adverse Events (summary data)
- Other Information
  - “Certain Agreements” Restricting Results Disclosure
  - Overall Limitations and Caveats
  - Results Point of Contact
Docetaxel in Breast Cancer

This study is ongoing, but not recruiting participants.

Study NCT00312208  Information provided by Sanofi-Aventis
Study First Received: April 5, 2006  Last Updated: February 15, 2010  History of Changes
Results First Received: October 29, 2009

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Interventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design:</td>
<td>Allocation: Randomized; Control: Active Control; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment</td>
</tr>
<tr>
<td>Condition:</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>Interventions:</td>
<td>Drug: docetaxel, doxorubicin, cyclophosphamide Drug: Docetaxel, doxorubicin, cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -&gt; T)</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>COMPLETED</td>
<td>1477</td>
</tr>
<tr>
<td>NOT COMPLETED</td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>97</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>4</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>3</td>
</tr>
<tr>
<td>Withdrawal by Subject</td>
<td>53</td>
</tr>
<tr>
<td>Not specified</td>
<td>5</td>
</tr>
</tbody>
</table>

[1] 1649 patients randomized, 1634 patients treated
[2] 1649 patients randomized 1635 patients treated
## Baseline Measures

<table>
<thead>
<tr>
<th></th>
<th>Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -&gt; T)</th>
<th>Docetaxel + Doxorubicin and Cyclophosphamide (TAC)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Participants</strong></td>
<td>1649</td>
<td>1649</td>
<td>3298</td>
</tr>
<tr>
<td>[units: participants]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age, Customized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[units: Participants]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 65 years</td>
<td>85</td>
<td>83</td>
<td>168</td>
</tr>
<tr>
<td>Between 65 and 50 years</td>
<td>784</td>
<td>783</td>
<td>1567</td>
</tr>
<tr>
<td>Between 49 and 35 years</td>
<td>689</td>
<td>710</td>
<td>1399</td>
</tr>
<tr>
<td>&lt;= 35 years</td>
<td>91</td>
<td>73</td>
<td>164</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[units: years]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Full Range)</td>
<td>50 (22 to 74)</td>
<td>50 (24 to 72)</td>
<td>50</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[units: participants]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1649</td>
<td>1649</td>
<td>3298</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Region of Enrollment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[units: participants]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal Receptor Status [Units: Participants]</td>
<td>User-Specified Baseline Measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1348</td>
<td>1346</td>
<td>2694</td>
</tr>
<tr>
<td>Negative</td>
<td>301</td>
<td>303</td>
<td>604</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Karnofsky Performance Status at Baseline [units: Participants]</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 - Activity with effort; some signs of disease</td>
</tr>
<tr>
<td>90 - Normal activity; minor signs of disease</td>
</tr>
<tr>
<td>100 - Normal no complaints; no evidence of disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Menopausal status [units: Participants]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Menopausal or Other age &lt; 50 Years</td>
</tr>
<tr>
<td>Post-Menopausal or Other age &gt; 50 Years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Positive Lymph Nodes [units: Participants]</th>
</tr>
</thead>
<tbody>
<tr>
<td>[0]</td>
</tr>
<tr>
<td>[1 to 3]</td>
</tr>
<tr>
<td>[4 to 10]</td>
</tr>
<tr>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with at least one surgery [units: Participants]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
</tr>
<tr>
<td>Lumpectomy</td>
</tr>
<tr>
<td>Quadrantectomy/Segmental</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Tumor [units: Participants]</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1: Tumor &lt; = 2cm</td>
</tr>
<tr>
<td>pT2: Tumor in [ 2 - 5 ]</td>
</tr>
<tr>
<td>pT3: Tumor &gt; 5cm</td>
</tr>
<tr>
<td>pT4: Tumor with extension to chest</td>
</tr>
</tbody>
</table>
Primary Outcome Measure: Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause (Disease-Free Survival)
[ Time Frame: Median follow-up 65 months ]

<table>
<thead>
<tr>
<th>Measured Values</th>
<th>Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -&gt; T)</th>
<th>Docetaxel + Doxorubicin and Cyclophosphamide (TAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants Analyzed [units: participants]</td>
<td>1649</td>
<td>1649</td>
</tr>
<tr>
<td>Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause (Disease-Free Survival) [units: Participants]</td>
<td>356</td>
<td>352</td>
</tr>
</tbody>
</table>

Statistical Analysis 1 for Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause (Disease-Free Survival)

<table>
<thead>
<tr>
<th>Groups [1]</th>
<th>All groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method [2]</td>
<td>Log Rank</td>
</tr>
<tr>
<td>P Value [3]</td>
<td>0.978</td>
</tr>
<tr>
<td>Hazard Ratio (HR) [4]</td>
<td>1.00</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(0.86 to 1.16)</td>
</tr>
</tbody>
</table>
Secondary Outcome Measure: Death From Any Cause (Overall Survival)  
[ Time Frame: Median follow-up of 65 months ]

<table>
<thead>
<tr>
<th>Measured Values</th>
<th>Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -&gt; T)</th>
<th>Docetaxel + Doxorubicin and Cyclophosphamide (TAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants Analyzed</td>
<td>1649</td>
<td>1649</td>
</tr>
<tr>
<td>[units: participants]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death From Any Cause (Overall Survival)</td>
<td>187</td>
<td>202</td>
</tr>
<tr>
<td>[units: Participants]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical Analysis 1 for Death From Any Cause (Overall Survival)

<table>
<thead>
<tr>
<th>Groups [1]</th>
<th>All groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method [2]</td>
<td>Log Rank</td>
</tr>
<tr>
<td>P Value [3]</td>
<td>0.371</td>
</tr>
<tr>
<td>Hazard Ratio (HR) [4]</td>
<td>0.91</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(0.75 to 1.11)</td>
</tr>
</tbody>
</table>
## Serious Adverse Events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -&gt; T)</th>
<th>Docetaxel + Doxorubicin and Cyclophosphamide (TAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, serious adverse events</td>
<td>331/1634 (20.26%)</td>
<td>520/1635 (31.80%)</td>
</tr>
<tr>
<td># participants affected / at risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Blood and lymphatic system disorders

- **Anemia**
  - # participants affected / at risk: 3/1634 (0.18%) 5/1635 (0.31%)
- **Coagulation disorders**
  - # participants affected / at risk: 1/1634 (0.06%) 0/1635 (0.00%)
- **Hemorrhage Vaginal**
  - # participants affected / at risk: 1/1634 (0.06%) 0/1635 (0.00%)
- **Leukopenia**
  - # participants affected / at risk: 18/1634 (1.10%) 56/1635 (3.43%)
- **Lymphadenopathy**
  - # participants affected / at risk: 0/1634 (0.00%) 1/1635 (0.06%)
- **Lymphedema**
  - # participants affected / at risk: 0/1634 (0.00%) 2/1635 (0.12%)
- **Pancytopenia**
  - # participants affected / at risk: 0/1634 (0.00%) 1/1635 (0.06%)
- **Thrombocytopenia**
  - # participants affected / at risk: 0/1634 (0.00%) 1/1635 (0.06%)

### Cardiac disorders

- **Arrhythmia**
  - # participants affected / at risk: 3/1634 (0.18%) 3/1635 (0.18%)
- **Arrhythmia Ventricular**

† Events were collected by systematic assessment
1 Term from vocabulary, COSTART
Certain Agreements

“Whether there exists an agreement (other than an agreement solely to comply with applicable provisions of law protecting the privacy of participants) between the sponsor or its agent and the principal investigator (unless the sponsor is an employer of the principal investigator) that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.”

[Sec. 282(j)(3)(C)(iv)]
Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

- The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

- The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

**Restriction Description:** If no publication has occurred within 12 months of the completion of the study, the Investigator shall have the right to publish/present independently the results of the study. The Investigator shall provide the Sponsor with a copy of any such presentation/publication for comment at least 30 days before any presentation/submission for publication. If requested by the Sponsor, any presentation/submission shall be delayed up to 90 days, to allow the Sponsor to preserve its proprietary rights.
Public Archive for Records

- Changes can and should be made to records
  - Estimated dates become “actual” dates
  - Estimated enrollment becomes “actual”
  - Other protocol changes
  - Overall recruitment status changes
  - Results may be added or changed

- All changes are publicly “tracked”
How Are Results Reported?

• Tables are “constructed” by the data provider
  – Columns are pre-set as study arms, but can be changed by the data provider
  – Rows are measures—some are pre-set, others are customized for each study
  – Type of measure determines specific design of “cells”

• Attempt to balance fixed structure with flexibility
### Edit Outcome Measure

**Title:** Crossover Study Example: Drug A vs. Placebo  
**ID:** 1122

<table>
<thead>
<tr>
<th><strong>Outcome Measure Type</strong></th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome Measure Reporting Status</strong></td>
<td>Posted</td>
</tr>
</tbody>
</table>
| **Anticipated Posting Date** | If the Reporting Status is "Not Posted", please enter a month and 4 digit year for the anticipated posting date.  
  **Month:** -- Please Select --  
  **Year:** |
| **Outcome Measure Title** | change in diastolic blood pressure |
| **Outcome Measure Time Frame** | 3 months |
| **Outcome Measure Description** | -- Please Select --  
  Mean  
  Median  
  Least Squares Mean  
  Geometric Mean  
  Log Mean |
| **Safety Issue** | FDAAAC |
| **Measure Type** | Mean |
| **Measure of Dispersion** | Please select "Not Applicable" if the Measure Type is "Number". Please do NOT select "Not Applicable" for other measure types.  
  **95% Confidence Interval** |
| **Unit of Measure** | -- Please Select --  
  Number  
  Not Applicable  
  Standard Deviation  
  Inter-Quartile Range  
  Full Range  
  Standard Error  
  95% Confidence Interval |
P-Value: (e.g. <0.01) <0.04

If desired, provide additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance.

Two-sided

Method: Other

If other, please specify: Paired t-test

If desired, provide additional information, such as adjustments or degrees of freedom.
## Statistics on Registration and Results Reporting by Data Provider Class (as of 12/2010)

<table>
<thead>
<tr>
<th>Data Provider</th>
<th>FDAAA Registration Analysis</th>
<th>FDAAA Results Analysis</th>
<th>All Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Registered Applicable Clinical Trials (ACTs)</td>
<td>“Responsible Party” Listed</td>
<td>“Primary Completion Date” Listed</td>
</tr>
<tr>
<td>Industry</td>
<td>14,609</td>
<td>12,057 (83%)</td>
<td>11,387 (78%)</td>
</tr>
<tr>
<td>NIH</td>
<td>5,450</td>
<td>1,894 (35%)</td>
<td>2,605 (48%)</td>
</tr>
<tr>
<td>Other</td>
<td>18,179</td>
<td>15,677 (86%)</td>
<td>15,506 (85%)</td>
</tr>
<tr>
<td>NCI</td>
<td>3,681</td>
<td>838 (23%)</td>
<td>1,553 (42%)</td>
</tr>
</tbody>
</table>

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1. All data as of November 3, 2010
2. Includes registered interventional studies of drugs, biologics, and devices that are “not phase 0/1” with either a Primary Completion Date ≥1/2008 or Study Completion Date > 1/2008 or both completion dates missing.
3. Based on estimated registered Applicable Clinical Trials with a Primary Completion Date prior to December 2009.
4. Submitted includes all “posted” and “not yet posted” records that may not be subject to FDAAA. Results are reviewed by NLM prior to posting and most records require one or more revisions.
Issues in Reporting Results
“…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.”

[NOTE: About 53% of results records have associated publications in PubMed (11/2010)]
Quality Standards

• Tables should convey study design, conduct and analysis

• Data must make sense
  – Measure name, units, and data must match
  – No invalid entries
  – No illogical tables
  – No missing parameters or data
NEED FOR RIGOR AND PRECISION

Source: http://xkcd.com/552/
Problems with Entries

- Unclear/imprecise entries (% reduction: - 40%)
- Illogical entries (time to survival)
- Internal inconsistencies (enrollment does not match participant flow)
- Invalid entries (823 hours/day sleep)
- Data mismatch (time to response: 12 participants)
- Structure does not make sense
  - arms (and participants) come and go
- Inconsistent with other information about study
  - Randomized studies cannot have only one arm
Ambiguity of Language

Term
• “Frequency”
• “Rate”
• “Incidence” (for # participants)
• “Percentage”

Entered Value
• “33”
  – People?
  – Weekly events?
  – Percent?

• “0.75”
  – 75%?
  – 0.75%?
Outcome Measure Statistics
ClinicalTrials.gov (as of 9/27/10)

- 2,178 Clinical trial results records posted
- 2,178 Records with 4,376 Primary OMs
  - Mean: 2.0
  - Median: 1
  - Range: 1-71
- 1,639 Records w/ 12,509 Secondary OMs
  - Mean: 5.7
  - Median: 3
  - Range: 0-122

“Other Pre-specified”: 119 Records, 424 OMs, Range: 0-31
“Post-Hoc”: 43 Records, 84 OMs, Range: 0-6
Level 1
Domain:

Level 2
Specific Measurement:
Beck Anxiety Inventory
Hamilton Anxiety Rating Scale
Fear Questionnaire

Level 3
Specific Metric:
End Value
Change from Baseline
Time to Event

Level 4
Method of Aggregation:
Continuous
Mean
Median
Proportion with Decrease ≥ 50%
Categorical
Proportion with Decrease ≥ 8 points
Structural Changes to Studies

• Arms come and go
• Participants come and go
• Participant Flow and Baseline Characteristics Tables describe different population than the Outcomes Tables
• Data providers cannot explain the “denominators”
<table>
<thead>
<tr>
<th>Variable</th>
<th>Abacavir–Lamivudine (N=398)</th>
<th>Tenofovir DF–Emtricitabine (N=399)</th>
<th>Total (N=797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>331 (83)</td>
<td>345 (86)</td>
<td>676 (85)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (17)</td>
<td>54 (14)</td>
<td>121 (15)</td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>38</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>32–45</td>
<td>32–46</td>
<td>32–45</td>
</tr>
<tr>
<td>Age group — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–19 yr</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>20–29 yr</td>
<td>77 (19)</td>
<td>68 (17)</td>
<td>145 (18)</td>
</tr>
<tr>
<td>30–39 yr</td>
<td>143 (36)</td>
<td>121 (30)</td>
<td>264 (33)</td>
</tr>
<tr>
<td>40–49 yr</td>
<td>121 (30)</td>
<td>142 (36)</td>
<td>263 (33)</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>41 (10)</td>
<td>54 (14)</td>
<td>95 (12)</td>
</tr>
<tr>
<td>&gt;59 yr</td>
<td>13 (3)</td>
<td>12 (3)</td>
<td>25 (3)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>170 (43)</td>
<td>202 (51)</td>
<td>372 (47)</td>
</tr>
<tr>
<td>Black</td>
<td>112 (28)</td>
<td>94 (24)</td>
<td>206 (26)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>103 (26)</td>
<td>93 (23)</td>
<td>196 (25)</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Native American or Alaskan Native</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Mixed race</td>
<td>7 (2)</td>
<td>3 (1)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Arms</td>
<td>Assigned Interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1: Experimental  
Participants will receive EFV, FTC/TDF, and placebo for ABC/3TC for 96 weeks | Drug: Efavirenz  
600 mg tablet taken orally daily  
Drug: Emtricitabine/Tenofovir disoproxil fumarate  
200 mg emtricitabine/300 mg tenofovir disoproxil fumarate tablet taken orally daily  
Drug: Abacavir/Lamivudine placebo  
Placebo tablet taken orally daily |
| 2: Experimental  
Participants will receive EFV, placebo for FTC/TDF, and ABC/3TC for 96 weeks | Drug: Abacavir/Lamivudine  
600 mg abacavir/300 mg lamivudine tablet taken orally daily  
Drug: Efavirenz  
600 mg tablet taken orally daily  
Drug: Emtricitabine/Tenofovir disoproxil fumarate placebo  
Placebo tablet taken orally daily |
| 3: Experimental  
Participants will receive RTV-boosted ATV, FTC/TDF, and placebo for ABC/3TC for 96 weeks | Drug: Atazanavir  
300 mg tablet taken orally daily  
Drug: Emtricitabine/Tenofovir disoproxil fumarate  
200 mg emtricitabine/300 mg tenofovir disoproxil fumarate tablet taken orally daily  
Drug: Ritonavir  
100 mg tablet taken orally daily  
Drug: Abacavir/Lamivudine placebo  
Placebo tablet taken orally daily |
| 4: Experimental  
Participants will receive RTV-boosted ATV, placebo for FTC/TDF, and ABC/3TC for 96 weeks | Drug: Abacavir/Lamivudine  
600 mg abacavir/300 mg lamivudine tablet taken orally daily  
Drug: Atazanavir  
300 mg tablet taken orally daily  
Drug: Ritonavir  
100 mg tablet taken orally daily  
Drug: Emtricitabine/Tenofovir disoproxil fumarate placebo  
Placebo tablet taken orally daily |
Stratification at Initial Screening

- **<100,000 HIV RNA**
  - Arm A
  - Arm B (+ABC)
  - Arm C
  - Arm D (+ABC)

- **≥100,000 HIV RNA**
  - Arm A
  - Arm B (+ABC)
  - Arm C
  - Arm D (+ABC)

**PLANNED**

**AMENDED by DSMB**

Ongoing Follow-up

- Arm A
- Arm B (+ABC)
- Arm C
- Arm D (+ABC)

Reported

- tenofovir DF–emtricitabine
- Abacavir (ABC)–lamivudine
Interventional or Observational?

• Key features of “interventional”
  – Investigator assigns participants to interventions
  – Interventions occur as the result of participation in a study with a protocol, and would not occur in the same manner if not in the study

• Example: Evaluation of PillCam™ Colon Capsule Endoscopy (PCCE) in the Visualization of the Colon
Alzheimer’s Study: Is this interventional?

- Longitudinal study of a cohort of adults at high risk of AD
- All participants receive several diagnostic tests at varying intervals, including:
  - Regular, periodic PET scan for the PiB marker
  - Comparison with MRI markers of small vessel disease
  - Assessment of cognitive decline in patients
Device or Procedure?

• What Is the Intervention Type?
  – Device vs. Procedure/Surgery (e.g., imaging)
  – Drug vs. Procedure (e.g., Cell Therapy)

• Example: The Stress Incontinence Surgical Treatment Efficacy Trial
  – Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence
  – Albo ME et al. NEJM (2007)
Studies Involving Genetic Tests

• Study Title: “Genotype Based Personalized Prescription of Nevirapine (GENPART)” [NCT00986063]
  – Primary Outcome Measure: “…incidences of nevirapine-associated rashes” between
    • Genetic Test Group: “nevirapine, guided by genetic tests”
    • Control Group: “standard of care approach”
  – Study of a Drug or Device (i.e., genetic test)?
Genetic Counseling in Women at Risk for BRCA1 or BRCA2 Mutations

This study is ongoing, but not recruiting participants.

First Received: December 27, 2006   Last Updated: March 7, 2009   History of Changes

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Lombardi Cancer Research Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborator</td>
<td>National Cancer Institute (NCI)</td>
</tr>
<tr>
<td>Information provided by</td>
<td>National Cancer Institute (NCI)</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00416754</td>
</tr>
</tbody>
</table>

Purpose

RATIONALE: Genetic counseling and using an interactive computer program may help women at risk for breast cancer make medical decisions about treatment.

PURPOSE: This randomized clinical trial is studying standard genetic counseling to see how well it works when given together with or without a medical decision-making computer program in women at risk for BRCA1 or BRCA2 mutations.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>Other: counseling intervention</td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Primary Purpose: Screening

Official Title: Improving the Long-Term Outcomes of BRCA1/BRCA2 Mutation Testing
Preliminary Findings: Fidelity to Protocol

• Structure of trial
  – Arms come and go
  – Participants come and go
  – Definition of “trial” is fluid

• Outcome measures
  – Primary vs. secondary vs. ???
  – Content of outcome measure

• Analysis Population
  – Up to 25 different “denominators” for a single study arm in a trial
  – 24% trials reported results involving ≤ 90% of all participants
Examples of Discrepant Primary Outcome Measures

• Specific Measure
  – “Time to progression” [unit of time] vs. “progression-free survival” [# participants]
  – “Time to the first [event]” vs. number of events
  – “[unprotected and protected] Sexual activities with main male partner” vs. unprotected only

• Time Frame
  – “fortnightly” [q 2 weeks] vs. “4 weeks”
  – “1 and 3 month post-injection” vs. “at one month”
The primary outcome measure was the change in the Hamilton Rating Scale for Depression (HAM-D) score from baseline to the end of the double-blind phase.
Preliminary Findings: Oversight
(Clinical Trial Results Records Posted on 9/27/10)

• 24% (359/1,509) reporting having a DMC*
  – By Phase**
    • 23% (125/535) – up to Phase 2
    • 27% (142/520) – Phase 2/3 or 3
    • 15% (45/298) – Phase 4
  – By Lead Sponsor Class
    • 17% (195/1,164) – Industry
    • 48% (164/345) – Non-Industry

• Of 1,730 reporting having “Certain Agreements”
  – 8% (132/1,730) impose embargoes ≤60 days
  – 16% (280/1,730) impose embargoes >60 and <180 days
  – 76% (1,318/1,730) describe “other” restrictions

*Optional data element
**156 records do not report Phase information
Issues to Consider in Determining Reporting Burden

• What’s the starting point?
  – Which data points are not routinely calculated or determined at the end of a study?

• Heterogeneity of trials
  – Complexity of trial design/structure
    – # arms (1-16)
    – # outcome measures (1-124)
    – # statistical analyses (0-50)

• Status of existing data management system
  – Many sponsors upload registry data
  – Others upload AEs
Minimal Results Data Set
(all results reported by arm)

- **Participant Flow**
  - Number Started
  - Number Completed

- **Baseline Characteristics**
  - Number of Participants
  - Age and Gender

- **Outcome Measures**
  - Summary results for Primary and Secondary OMs
  - Statistical analyses, as appropriate

- **Adverse Events**
  - “Serious” and “Other” by Organ System
Three Components of Successful Results Data Entry

• Familiarity with the system
  – Initial (steep) learning curve
• Clinical trial expertise
  – Including knowledge of specific trial
• Relevant data from the trial
Efforts to Improve Compliance

• Ongoing outreach and educational efforts
• Better resource materials
• Informational Messages
Sample Message
(FDAAAA Registration Data Element Missing)

ClinicalTrials.gov Records and FDAAAA Requirements

Message generated by ClinicalTrials.gov Protocol Registration System

NOTE: Each ClinicalTrials.gov record below either lists a date for the final data collection of the primary outcome measure (currently, the "Primary Completion Date" field in ClinicalTrials.gov) that is more than 12 months in the past or is missing an entry for this field. Please be aware that, under FDAAA, results of certain "applicable clinical trials" involving FDA-regulated drugs, biological products, or devices must be reported to ClinicalTrials.gov within 12 months of this date. The Responsible Party is encouraged to take the following steps, as appropriate, if this trial is an "applicable clinical trial":

a. check that the "Primary Completion Date" and other items in the registry record are accurate and update if necessary; and, if appropriate,

b. enter results in the PRS if required; OR

c. consider the "delayed reporting" options at http://prsinfo.clinicaltrials.gov/DelayedSubmission.html.
EMA Requirements

• Publically Accessible Results Database
  – Required no later than 6 months after trial completion (i.e., last patient, last visit)
  – Applies to EU-regulated clinical trials of medicines, regardless of authorization status
  – Applies to trials of pediatric and adult drugs

• Interaction to harmonize EudraCT and ClinicalTrials.gov databases & policies
Issues for Academic Medical Centers

- Legal/regulatory issues related to RP and compliance
- Support for PIs who must report data
  - Help with system training
  - Provide appropriate biostatistical support
- Are trials becoming too complex?
- Are roles clear? (Who is responsible?)
- Emphasize clinical epidemiology principles in student and researcher training programs
Bottom Line

• Determine who is the Responsible Party
• Register prior to enrollment (or within 21d):
  – Phase 2-4 interventional trials that include a drug, device or biologic
  – Regardless of whether or not the trial is being used to support an FDA application
• Report results:
  – Any trial described above once the drug, device or biologic has been approved; OR
  – Within one year of “primary completion date”
• Keep all information up to date!
In Sum

• National (international) experiment
• System before FDAAA was not working (with regard to dissemination of trial information)
• Structured database complements journal publications
• Requires and reinforces knowledge of basic principles of clinical epidemiology
• We are here to help
Resources
# Help for Users

**ClinicalTrials.gov Background Information**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding Clinical Trials</td>
<td>How clinical trials work, potential benefits and risks</td>
</tr>
<tr>
<td>About ClinicalTrials.gov</td>
<td>Background information, history and current status</td>
</tr>
<tr>
<td>ClinicalTrials.gov Results</td>
<td>Overview and availability</td>
</tr>
<tr>
<td>What’s New</td>
<td>Recently published trials; trials in the news</td>
</tr>
<tr>
<td><strong>Online Training</strong></td>
<td>Brief animated tutorials with audio on using ClinicalTrials.gov</td>
</tr>
<tr>
<td>Help</td>
<td>How-to information for finding trials in ClinicalTrials.gov</td>
</tr>
<tr>
<td>Glossary</td>
<td>Terms related to clinical trials</td>
</tr>
<tr>
<td>More Resources</td>
<td>Links to other sources of information on Clinical Trials</td>
</tr>
<tr>
<td>FDA Resources</td>
<td>Drug and Device information from the US Food and Drug Administration</td>
</tr>
<tr>
<td>Linking to Us</td>
<td>How to create links that search ClinicalTrials.gov</td>
</tr>
</tbody>
</table>

*http://clinicaltrials.gov/ct2/info*
ClinicalTrials.gov Online Training

The following are brief animated tutorials with audio for using the ClinicalTrials.gov. Running times are rounded to the nearest minute. Click on the link to launch the tour.

- Basic Search (3 min., March 2010)
- Clinical Study Details (2 min., March 2010)
- Customize Your Display (2 min., March 2010)
- Advanced Search (3 min., March 2010)
- Refine a Search (2 min., March 2010)
- Downloading Search Results (4 min., March 2010)
- RSS Feed Setup for a Search (2 min., March 2010)

The above demos require the Adobe Flash™ Player. They were created using Carbon Viewlet Builder™.

Last updated: 26 March 2010
First published: 26 March 2010
Metadata | Permanence level: Permanence Not Guaranteed
Next, click on the "Advanced Search" link below the search box or the tab at the top of the page.
Help for Trial Sponsors & Investigators

ClinicalTrials.gov
Protocol Registration System

Registration of Clinical Trials

Clinical trials are registered with ClinicalTrials.gov via a web-based data entry system called the Protocol Registration System (PRS).

ClinicalTrials.gov allows the reporting of trials that:
- Are in conformance with any applicable human subject or ethics review regulations (or equivalent) and
- Are in conformance with any applicable regulations of the national (or regional) health authority (or equivalent)

ClinicalTrials.gov facilitates registration of trials in accordance with the International Committee of Medical Journal Editors (ICMJE) initiative requiring prior entry of clinical trials in a public registry as a condition for publication.

Multi-site trials and multi-sponsor trials are susceptible to duplicate registration, thus care must be taken in how the trials are registered. For multi-sponsor trials it is the lead sponsor who should take responsibility for registration. It is critical that investigators and sponsors work together to ensure that a trial is registered once and only once.

http://prsinfo.clinicaltrials.gov
The International Committee of Medical Journal Editors (ICMJE) has established a requirement that all clinical trials be entered in a public registry before the onset of patient enrollment, as a condition of consideration for publication.

ClinicalTrials.gov provides a vehicle which allows organizations and individuals to provide the data requested by ICMJE, which has adopted the World Health Organization (WHO) minimal registration data set.

See the following ICMJE resources for more information:

ICMJE Web site
ICMJE FAQ on Trial Registration
Statement on Clinical Trial Registration (September 2004)
General Requirements

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

**Trials of Drugs and Biologics**: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

**Trials of Devices**: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

"Applicable clinical trials" generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE). For the complete statutory definitions and more detailed information on the agency’s current thinking about their meaning, see this pdf document.

http://prsinfo.clinicaltrials.gov/fdaaa.html
Additional Background


Additional Information

- Email LISTSERV and other FDAAA information:
  - http://prsinfo.clinicaltrials.gov/fdaaa.html
- Other general information:
  - http://prsinfo.clinicaltrials.gov
- Questions?
  - register@clinicaltrials.gov
"Basic Results" Database

- **Pre-Submission Checklist (pdf) (DRAFT)** - a short reminder checklist to assist in results data entry
- **Common errors (pdf) (DRAFT)** - overview of common types of errors identified in submitted records with "basic results"
- **Helpful hints (pdf)** - tips on entering results data, including three examples of common study models (parallel design, crossover design, and diagnostic accuracy studies), reporting measure types, including information on reporting outcomes measured with a scale.
- **"Basic Results" Data Element Definitions (DRAFT)** - details on the information that is entered about results via the PRS.
- **Detailed Review Items (pdf) (DRAFT)** - describes items evaluated by the Quality Assurance/Quality Control staff at ClinicalTrials.gov after results have completed high-level review.
- **Basic Results Provisions** - extracted from FDAAA 801.
- **Delayed Submission of Results** - information on submitting certifications or requests for extension
- **Recorded Presentation** (Adobe Flash: 37 minutes) and accompanying slides (pdf)
  - Module 1: ClinicalTrials.gov Overview and PL 110-85 Requirements
  - Module 2: "Basic Results" Data Entry
  - Module 3: Posted Results at ClinicalTrials.gov