

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Overview of ClinicalTrials.gov

Deborah A. Zarin, M.D.
Director, ClinicalTrials.gov
National Library of Medicine



<http://ClinicalTrials.gov>

Outline

- Rationale for clinical trial registration and results reporting
- ClinicalTrials.gov background
- Basics of results reporting
- ClinicalTrials.gov review process

2

What's All the Fuss About?

- Suppression of research results impedes the scientific process in all areas of science
- Suppression of clinical trial data is particularly problematic
 - Trials depend on human volunteers
 - Trial results inform our medical decisions

3

Three Key Problems

- Not all trials are published
- Publications do not always include all prespecified outcome measures
- Unacknowledged changes are made to the trial protocol that would affect the interpretation of the findings
 - e.g., changes to the prespecified outcome measures

4

Levels of “Transparency”



Zarin DA, Tse T. Science. 2008

5

Reasons To Register Clinical Trials and Report Results

- Human Subject Protections
 - Allows potential participants to find studies
 - Assists ethical review boards and others in determining appropriateness of studies being reviewed (e.g., harms, benefits, redundancy)
 - Promotes 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

6

ClinicalTrials.gov Background

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
 - Maine State Law, State Attorneys General
 - International Committee of Medical Journal Editors (ICMJE) statement (2004)
- ClinicalTrials.gov accommodates other policies
- 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

ClinicalTrials.gov Records

- One record per trial
- Registration
 - Submitted at trial initiation
 - Summarizes information from trial protocol
 - Includes recruitment information (e.g., eligibility, locations)
- Results
 - Submitted after trial completion
 - Summarizes trial results

9

Protocol Information

- Descriptive Information
 - Study Type, Phase, Design, Outcomes, Enrollment, Start and Completion Dates
- Recruitment Information
 - Eligibility Criteria, Overall and Individual Site Recruitment Status
- Location and Contact Information
 - Sponsor and/or Responsible Party
 - Facility Name and Contact
- Administrative data
 - Protocol ID
 - IND/IDE Number (not public)

10

Results Information

- Participant Flow
- Baseline and Demographic Characteristics
- Primary and Secondary Outcomes
- Adverse Event information
- Other Information
 - “Certain Agreements” related to restrictions on results disclosure
 - Overall Limitations and Caveats
 - Results Point of Contact

11

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”

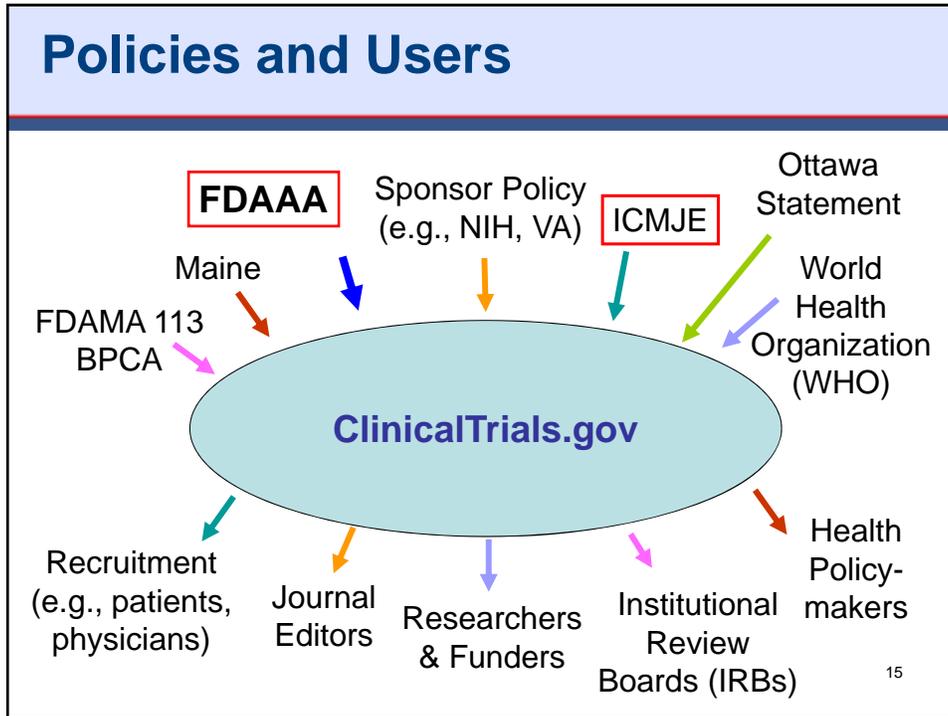
12

Trial Life Cycle

- Initial registration
- Updates, as necessary
 - Enrollment
 - Key dates
 - Recruitment status
 - Other protocol changes
- Initial results reporting
- Updates, as necessary

13

Key Policies and Laws



FDAAA

Sec. 801. Expanded Clinical Trial Registry Data Bank

- Enacted on September 27, 2007
- Requires trial registration
- Requires results reporting
- Added enforcement provisions
 - Notices of noncompliance
 - Civil monetary penalties (up to \$10,000/day)
 - Withholding of NIH grant funds

16

Registration Policies

- ICMJE*
 - Interventional trials
 - All intervention types
 - All phases
- FDAAA†
 - Interventional trials
 - Drugs, biologics, devices
 - Not phase 1 drug or not small feasibility device
 - US FDA jurisdiction (e.g., IND/IDE or U.S. site)

* Laine C, Horton R, DeAngelis C, et al. Ann Intern Med. 2007; http://www.icmje.org/faq_clinical.html

† <http://prsinfo.clinicaltrials.gov/fdaaa.html>

17

Results Reporting Policies— FDAAA

- Which trials?
 - Interventional trials
 - Drugs, biologics, devices
 - Once approved by FDA
 - Not phase 1 drug or not small feasibility device
 - U.S. FDA jurisdiction (e.g., IND/IDE or U.S. site)
- When?
 - Generally within 12 months of (primary) completion date
 - Delays possible

<http://prsinfo.clinicaltrials.gov/fdaaa.html>

18

FDAAA Key Terms

- Applicable Clinical Trials (ACTs)
 - Interventional trials (with 1 or more arms)
 - Not phase 1; includes drug, biologic, or device
 - At least one site in U.S. (or IND/IDE)
- ACTs initiated on or after 9/27/07 or ongoing as of 12/26/07
- Responsible Party
 - Sponsor, grantee OR
 - Principal Investigator (PI), if designated
- (Primary) Completion Date

<http://prsinfo.clinicaltrials.gov/fdaaa.html>

19

Results Reporting and Trial Publication

- 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

* Laine C, Horton R, DeAngelis C, et al. Ann Intern Med. 2007; http://www.icmje.org/faq_clinical.html

20

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary

Search

Full Text View Tabular View No Study Results Posted Related Studies

CATIE-Alzheimer's Disease Trial

This study has been completed.

First Received: April 20, 2001 Last Updated: February 11, 2009 [History of Changes](#)

| | |
|--------------------------------|--|
| Sponsor: | National Institute of Mental Health (NIMH) |
| Information provided by: | National Institute of Mental Health (NIMH) |
| ClinicalTrials.gov Identifier: | NCT00015548 |

More Information

Additional Information:

[Click here to find more information about the study.](#)

[More information about Alzheimer's Disease](#)

Publications:

Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA. CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med.* 2006 Oct 12;355(15):1525-38.

Schneider LS, Tariot PN, Lyketsos CG, Dagerman KS, Davis KL, Davis S, Hsiao JK, Jeste DV, Katz IR, Olin JT, Pollock BG, Rabins PV, Rosenheck RA, Small GW, Lebowitz B, Lieberman JA. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). Alzheimer disease trial methodology. *Am J Geriatr Psychiatry.* 2001 Fall;9(4):346-60.

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary

PubMed.gov

Search: PubMed Limits Advanced search Help

Search Clear

Full Text View

Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease.

Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA. CATIE-AD Study Group. *Kock School of Medicine, University of Southern California, Los Angeles, CA 90033, USA; lschneid@usc.edu*

Abstract

BACKGROUND: Second-generation (atypical) antipsychotic drugs are widely used to treat psychosis, aggression, and agitation in patients with Alzheimer's disease, but their benefits are uncertain and concerns about safety have emerged. We assessed the effectiveness of atypical antipsychotic drugs in outpatients with Alzheimer's disease.

METHODS: In this 42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks.

RESULTS: There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) (P=0.52). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) (P=0.002). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received placebo discontinued their assigned treatment owing to intolerability (P=0.009). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo (P=0.22).

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 [ClinicalTrials.gov]).

Copyright 2006 Massachusetts Medical Society.

Publications:

Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA. CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med.* 2006 Oct 12;355(15):1525-38.

Schneider LS, Tariot PN, Lyketsos CG, Dagerman KS, Davis KL, Davis S, Hsiao JK, Jeste DV, Katz IR, Olin JT, Pollock BG, Rabins PV, Rosenheck RA, Small GW, Lebowitz B, Lieberman JA. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). Alzheimer disease trial methodology. *Am J Geriatr Psychiatry.* 2001 Fall;9(4):346-60.

Secondary Source ID:
ClinicalTrials.gov/NCT00015548

The screenshot shows a ClinicalTrials.gov record for a study titled "Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease". The record is displayed as a "Full Text View" of a journal article abstract from The New England Journal of Medicine. The article title is "Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease". The authors listed are 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. The abstract includes sections for Background, Methods, Results, and Conclusions. The Conclusions section states: "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.)". The ClinicalTrials.gov number is highlighted with a red box. The record also includes a "Secondary Source ID" field with the value "ClinicalTrials.gov/NCT00015548" and a "Publications" section with a link to the full text.

Sample Posted Record*

*Adapted from NCT00312208

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary

Study 1 of 1 for search of: NCT00312208

Previous Study Return to Search Results Next Study

Full Text View Tabular View Study Results Related Studies

Docetaxel in Breast Cancer

This study is ongoing, but not recruiting participants.

First Received: April 5, 2006 Last Updated: February 15, 2010 [History of Changes](#)

| | |
|--------------------------------|-------------------------------------|
| Sponsor: | Sanofi-Aventis |
| Collaborator: | Cancer International Research Group |
| Information provided by: | Sanofi-Aventis |
| ClinicalTrials.gov Identifier: | NCT00312208 |

25

Full Text View Tabular View Study Results Related Studies

Docetaxel in Breast Cancer

This study is ongoing, but not recruiting participants.

First Received: April 5, 2006 Last Updated: February 15, 2010 [History of Changes](#)

| | |
|--------------------------------|-------------------------------------|
| Sponsor: | Sanofi-Aventis |
| Collaborator: | Cancer International Research Group |
| Information provided by: | Sanofi-Aventis |
| ClinicalTrials.gov Identifier: | NCT00312208 |

Purpose

Primary objective :

- To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide to doxorubicin and cyclophosphamide followed by docetaxel in operable adjuvant breast cancer HER2neu negative patients with positive axillary lymph nodes.

Secondary objectives :

- To compare toxicity and quality of life between the 2 above-mentioned arms.
- To evaluate pathologic and molecular markers for predicting efficacy.

| Condition | Intervention | Phase |
|---------------|---|-----------|
| Breast Cancer | Drug: docetaxel, doxorubicin, cyclophosphamide Drug: Docetaxel,doxorubicin, cyclophosphamide | Phase III |

Study Type: Interventional
Study Design: Allocation: Randomized
Control: Active Control

26

Condition: Breast Cancer

Study Type: Interventional

Study Design: Allocation: Control: Active

Endpoint Classification: Interventional

Masking: Open Label

Primary Purpose: Treatment

Official Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Cyclophosphamide in the Adjuvant Treatment of Breast Cancer

Resource links provided:

[Genetics Home Reference](#)

[MedlinePlus related topics](#) [Breast Cancer](#) [Cancer](#)

[Drug Information](#) available for: [Cyclophosphamide](#) [Doxorubicin](#) [Doxorubicin hydrochloride](#) [Docetaxel](#)

[U.S. FDA Resources](#)

The screenshot shows the MedlinePlus website interface. At the top, there is a search bar and navigation tabs for 'Health Topics', 'Drugs & Supplements', and 'Videos & Cool Tools'. Below these, a list of 'Other Topics' includes 'Breast Cancer', which is circled in red. The main content area features an article about breast cancer, including a purple awareness ribbon image and a 'MEDICAL ENCYCLOPEDIA' section.

27

Full Text View
Tabular View
Study Results
Related Studies

Docetaxel in Breast Cancer

This study is ongoing, but not recruiting participants.

Study NCT00312208 Information provided by Sanofi-Aventis
 First Received: April 5, 2006 Last Updated: February 15, 2010 [History of Changes](#)

| Tracking Information | |
|--|--|
| First Received Date <small>ICMJE</small> | April 5, 2006 |
| Last Updated Date | February 15, 2010 |
| Start Date <small>ICMJE</small> | August 2000 |
| Primary Completion Date | October 2008 (final data collection date for primary outcome measure) |
| Current Primary Outcome Measures <small>ICMJE</small> <small>(submitted: February 15, 2010)</small> | Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause [Time Frame: Median follow-up 65 months] [Designated as safety issue: No] |
| Original Primary Outcome Measures <small>ICMJE</small> <small>(submitted: January 25, 2008)</small> | Disease-Free Survival (DFS) [Time Frame: interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer (or death from any cause whichever occurs first)] |
| Change History | Complete list of historical versions of study NCT00312208 on ClinicalTrials.gov Archive Site |

28

[Full Text View](#) [Tabular View](#) **Study Results** [Related Studies](#)

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

| | |
|-----------------------|--|
| Study Type: | Interventional |
| Study Design: | Allocation: Randomized; Control: Active Control; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment |
| Condition: | Breast Cancer |
| Interventions: | Drug: docetaxel, doxorubicin, cyclophosphamide Drug: Docetaxel, doxorubicin, cyclophosphamide |

29

Participant Flow

“A table..., including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any.”

[Sec. 282(j)(3)(C)(i)]

| Participant Flow: Overall Study | | |
|---------------------------------|--|--|
| | Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T) | Docetaxel + Doxorubicin and Cyclophosphamide (TAC) |
| STARTED | 1649 ^[1] | 1649 ^[2] |
| COMPLETED | 1477 | 1526 |
| NOT COMPLETED | 172 | 123 |
| Adverse Event | 97 | 61 |
| Protocol Violation | 5 | 3 |
| Death | 2 | 1 |
| Lack of Efficacy | 7 | 4 |
| Lost to Follow-up | 3 | 5 |
| Withdrawal by Subject | 53 | 42 |
| Not specified | 5 | 7 |

Reasons Not Completed

[1] 1649 patients randomized, 1634 patients treated
 [2] 1649 patients randomized 1635 patients treated

31

Baseline Measures

“A table of the demographic and baseline data collected overall and for each arm of the clinical trial...”

[Sec. 282(j)(3)(C)(i)]

| Baseline Measures | | | |
|--|--|--|--------------------|
| | Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T) | Docetaxel + Doxorubicin and Cyclophosphamide (TAC) | Total |
| Number of Participants [units: participants] | 1649 | 1649 | 3298 |
| Age, Customized [units: Participants] | | | |
| > =65 years | 85 | 83 | 168 |
| Between 65 and 50 years | 784 | 783 | 1567 |
| Between 49 and 35 years | 689 | 710 | 1399 |
| < =35 years | 91 | 73 | 164 |
| Age [units: years] Median (Full Range) | 50 (22 to 74) | 50 (24 to 72) | 50 (22 to 74) |
| Gender [units: participants] | | | |
| Female | 1649 | 1649 | 3298 |
| Male | 0 | 0 | 0 |
| Region of Enrollment [units: participants] | | | 33 |

“Default” Required Measures

| User-Specified Baseline Measures | | | |
|--|------|------|------|
| Hormonal Receptor Status [units: Participants] | | | |
| Positive | 1348 | 1346 | 2694 |
| Negative | 301 | 303 | 604 |
| Karnofsky Performance Status at Baseline [units: Participants] | | | |
| 80 - Activity with effort; some signs of disease | 36 | 33 | 69 |
| 90 - Normal activity; minor signs of disease | 315 | 323 | 638 |
| 100 - Normal no complaints; no evidence of disease | 1298 | 1293 | 2591 |
| Menopausal status [units: Participants] | | | |
| Pre-Menopausal or Other age < 50 Years | 866 | 863 | 1729 |
| Post-Menopausal or Other age > 50 Years | 783 | 786 | 1569 |
| Number of Positive Lymph Nodes [units: Participants] | | | |
| [0] | 0 | 1 | 1 |
| [1 to 3] | 1010 | 1005 | 2015 |
| [4 to 10] | 462 | 456 | 918 |
| > 10 | 177 | 187 | 364 |
| Patients with at least one surgery [units: Participants] | | | |
| Mastectomy | 955 | 973 | 1928 |
| Lumpectomy | 283 | 276 | 559 |
| Quadrantectomy/Segmental | 411 | 400 | 811 |
| Primary Tumor [units: Participants] | | | |
| pT1: Tumor < = 2cm | 692 | 668 | 1360 |
| pT2: Tumor in [2 - 5] | 824 | 844 | 1668 |
| pT3: Tumor > 5cm | 131 | 135 | 266 |
| pT4: Tumor with extension to chest | | | |

34

Outcome Measure

“...a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial...”

[Sec. 282(j)(3)(C)(ii)]

35

Statistical Analysis

“...a table of values for each of the primary and secondary outcome measures..., including the results of scientifically appropriate tests of the statistical significance of such outcome measures.”

[Sec. 282(j)(3)(C)(ii)]

36

Primary Outcome Measure

Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause
 [Time Frame: Median follow-up 65 months]

Measured Values

| | Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T) | Docetaxel + Doxorubicin and Cyclophosphamide (TAC) |
|--|--|--|
| Number of Participants Analyzed [units: participants] | 1649 | 1649 |
| Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause [units: Participants] | 356 | 352 |

Statistical Analysis 1 for Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause

| | |
|---|------------------|
| Groups ^[1] | All groups |
| Method ^[2] | Log Rank |
| P Value ^[3] | 0.978 |
| Hazard Ratio (HR) ^[4] | 1.00 |
| 95% Confidence Interval | (0.86 to 1.16) |

37

Secondary Outcome Measure

Death From Any Cause
 [Time Frame: Median follow-up of 65 months]

Measured Values

| | Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T) | Docetaxel + Doxorubicin and Cyclophosphamide (TAC) |
|---|--|--|
| Number of Participants Analyzed [units: participants] | 1649 | 1649 |
| Death From Any Cause [units: Participants] | 187 | 202 |

Statistical Analysis 1 for Death From Any Cause

| | |
|---|------------------|
| Groups ^[1] | All groups |
| Method ^[2] | Log Rank |
| P Value ^[3] | 0.371 |
| Hazard Ratio (HR) ^[4] | 0.91 |
| 95% Confidence Interval | (0.75 to 1.11) |

38

Serious Adverse Events

“A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial.”

[Sec. 282(j)(3)(I)(iii)(I)]

39

| Serious Adverse Events | | |
|--|---|--|
| | Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC → T) | Docetaxel + Doxorubicin and Cyclophosphamide (TAC) |
| Total, serious adverse events | | |
| # participants affected / at risk | 331/1634 (20.26%) | 520/1635 (31.80%) |
| Blood and lymphatic system disorders | | |
| Anemia † ¹ | | |
| # participants affected / at risk | 3/1634 (0.18%) | 5/1635 (0.31%) |
| Coagulation disorders † ¹ | | |
| # participants affected / at risk | 1/1634 (0.06%) | 0/1635 (0.00%) |
| Hemorrhage Vaginal † ¹ | | |
| # participants affected / at risk | 1/1634 (0.06%) | 0/1635 (0.00%) |
| Leukopenia † ¹ | | |
| # participants affected / at risk | 18/1634 (1.10%) | 56/1635 (3.43%) |
| Lymphadenopathy † ¹ | | |
| # participants affected / at risk | 0/1634 (0.00%) | 1/1635 (0.06%) |
| Lymphedema † ¹ | | |
| # participants affected / at risk | 0/1634 (0.00%) | 2/1635 (0.12%) |
| Pancytopenia † ¹ | | |
| # participants affected / at risk | 0/1634 (0.00%) | 1/1635 (0.06%) |
| Thrombocytopenia † ¹ | | |
| # participants affected / at risk | 0/1634 (0.00%) | 1/1635 (0.06%) |
| Cardiac disorders | | |
| Arrhythmia † ¹ | | |
| # participants affected / at risk | 3/1634 (0.18%) | 3/1635 (0.18%) |
| Arrhythmia Ventricular † ¹ | | |
| | | |
| † Events were collected by systematic assessment ¹ Term from vocabulary, COSTART | | |

40

Frequent Adverse Events

“A table of anticipated and unanticipated adverse events **that are not included in the [Serious Adverse Events] table**...that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial.”

[Sec. 282(j)(3)(I)(iii)(II)]

41

| Other Adverse Events | | |
|--|--|--|
| | Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T) | Docetaxel + Doxorubicin and Cyclophosphamide (TAC) |
| Total, other (not including serious) adverse events | | |
| # participants affected / at risk | 1634/1634 | 1629/1635 |
| Blood and lymphatic system disorders | | |
| Anemia † ² | | |
| # participants affected / at risk | 461/1634 (28.21%) | 658/1635 (40.24%) |
| Epistaxis † ¹ | | |
| # participants affected / at risk | 123/1634 (7.53%) | 72/1635 (4.40%) |
| Leucopenia † ¹ | | |
| # participants affected / at risk | 59/1634 (3.61%) | 88/1635 (5.38%) |
| Lymphedema † ¹ | | |
| # participants affected / at risk | 101/1634 (6.18%) | 109/1635 (6.67%) |
| Neutropenia † ² | | |
| # participants affected / at risk | 1133/1634 (69.34%) | 1049/1635 (64.16%) |
| † Events were collected by systematic assessment 1 Term from vocabulary, COSTART 2 Term from vocabulary, NCI-CTCAE | | |

42

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)]

43

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.

44

ClinicalTrials.gov Review Criteria

Protocol/Results Review Criteria

- Protocol and results must be clear and informative
- Review focuses on:
 - Logic and internal consistency
 - Apparent validity
 - Meaningful entries
 - Formatting

PRS Information Resources

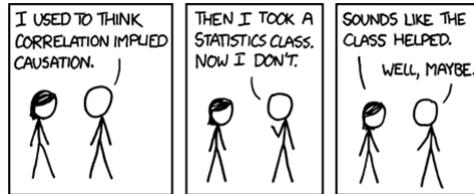
- Protocol Registration
 - Data Elements
 - Detailed Review Items
- Results
 - Data Elements
 - Detailed Review Items
 - Pre-submission Checklist
 - Helpful Hints and Common Errors
- User's Guide [PRS Main Menu]

<http://prsinfo.clinicaltrials.gov/fdaaa.html>

47

Problems Detected in Results Records

Need for Rigor and Precision



<http://xkcd.com/552/>

49

Invalid Entry

| | Intervention X | Control |
|--|----------------|---------------|
| Number of Participants Analyzed [units: Participants] | 28 | 27 |
| Hours Per Day of Sleep [units: Average Hours per Day] Mean \pm Standard Deviation | 823 \pm 92 | 864 \pm 106 |

50

Internal Inconsistency

Double Blind Treatment

| | Drug | Placebo |
|--------------------|------|---------|
| STARTED | 299 | 303 |
| Received Treatment | 297 | 302 |
| COMPLETED | 0 | 0 |
| Not Completed | 299 | 303 |

?

| | Drug | Placebo |
|---------------|------|---------|
| STARTED | 151 | 140 |
| COMPLETED | 0 | 0 |
| Not Completed | 151 | 140 |

?

| | Drug | Placebo |
|---------------|------|---------|
| STARTED | 57 | 47 |
| COMPLETED | 0 | 0 |
| Not Completed | 57 | 47 |

51

**“This isn't right.
This isn't even wrong.”**

Wolfgang Pauli, on a paper submitted by a physicist colleague;
Swiss (Austrian-born) physicist (1900–1958)

Informative Entry

| | |
|----------------------------|---|
| Measure Name | Pregnancy Rate (Pearl Index) |
| Measure Description | Pearl Index = $(100) * (\text{number of pregnancies}) * (4 \text{ cycles/year}) / \text{number of 91-day cycles completed}$. |
| Time Frame | After the onset of treatment and within 14 days after the last combination pill (approx. 1 year of treatment) |

| | |
|--|----------------|
| | DR-1011 |
| Number of Participants Analyzed | 1,735 |
| Pregnancy Rate (Pearl Index) [units: Pregnancies per 100 Women Years Exposure] | 2.74 |

53

Issues in Reporting Results

Experience With Results Database

- Entering results is similar to writing a journal article
- Data provider must be able to understand the study design and data analysis
 - Typically, the investigator and/or a statistician will need to be involved

55

Who Is the Audience?



PI and clinical research team

Other medical researchers in same field

Other medical researchers in other fields

Other readers of the medical literature

Science writers

Lay public (readers of consumer health literature)

56

Clarifications About Results Reporting Requirements

- Intended audience vs. intended beneficiaries
- FDAAA mandates pertain to reporting, not to conduct of clinical trials
- Results reporting to ClinicalTrials.gov complements journal publication

57

ICMJE Policy

“...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: Only about 53 percent of posted results records have associated publications]

Laine C, Horton R, DeAngelis C, et al. *Ann Intern Med.* 2007

58

Sample Uses of ClinicalTrials.gov

- Access information about specific trial
 - Track progress and protocol changes
 - See results
- Assess available evidence relevant to a specific clinical topic
- Assess nature of current and past research in a given area
- Review methodologies used in clinical trials

59

Select Publications

Tse T, Williams RJ, Zarin DA. Update on registration of clinical trials in ClinicalTrials.gov. *Chest* 2009;136:304-5.

Tse T, Williams RJ, Zarin DA. Reporting basic results in ClinicalTrials.gov. *Chest* 2009;136:295-303.

Zarin DA, Tse T. Moving toward transparency of clinical trials. *Science* 2008;319:1340-2.

Wood AJ. Progress and deficiencies in the registration of clinical trials. *N Engl J Med* 2009;360:824-30.

60

Additional Information

General ClinicalTrials.gov information:

<http://prsinfo.clinicaltrials.gov>

FDAAA-related information:

<http://prsinfo.clinicaltrials.gov/fdaaa.html>

Office of Extramural Research:

http://grants.nih.gov/Clinicaltrials_fdaaa/

Questions?

register@clinicaltrials.gov