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

Overview of ClinicalTrials.gov

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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

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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

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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

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Levels of "Transparency"

Zarin DA, Tse T. Science. 2008

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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

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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

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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

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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)

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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

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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"

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Trial Life Cycle

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

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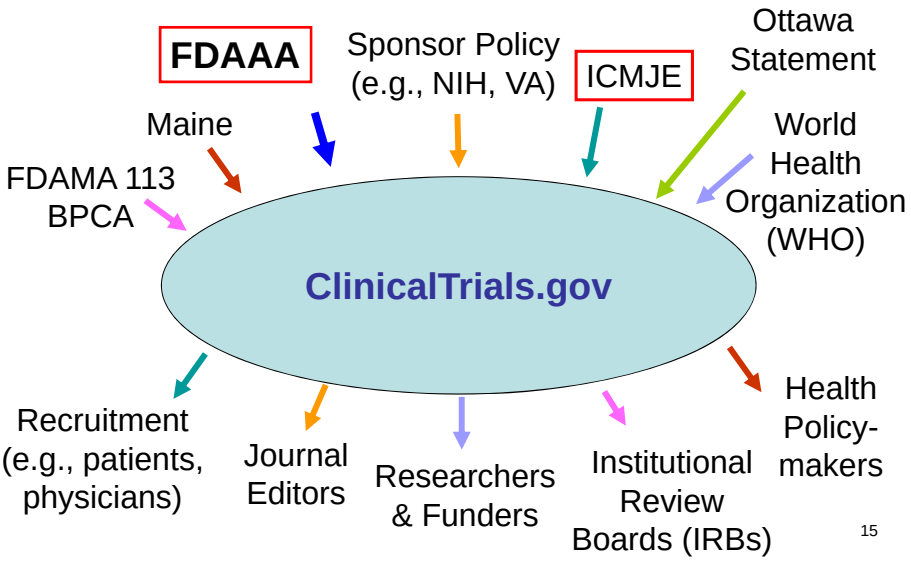
Key Policies and Laws

Policies and Users



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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

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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

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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

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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

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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

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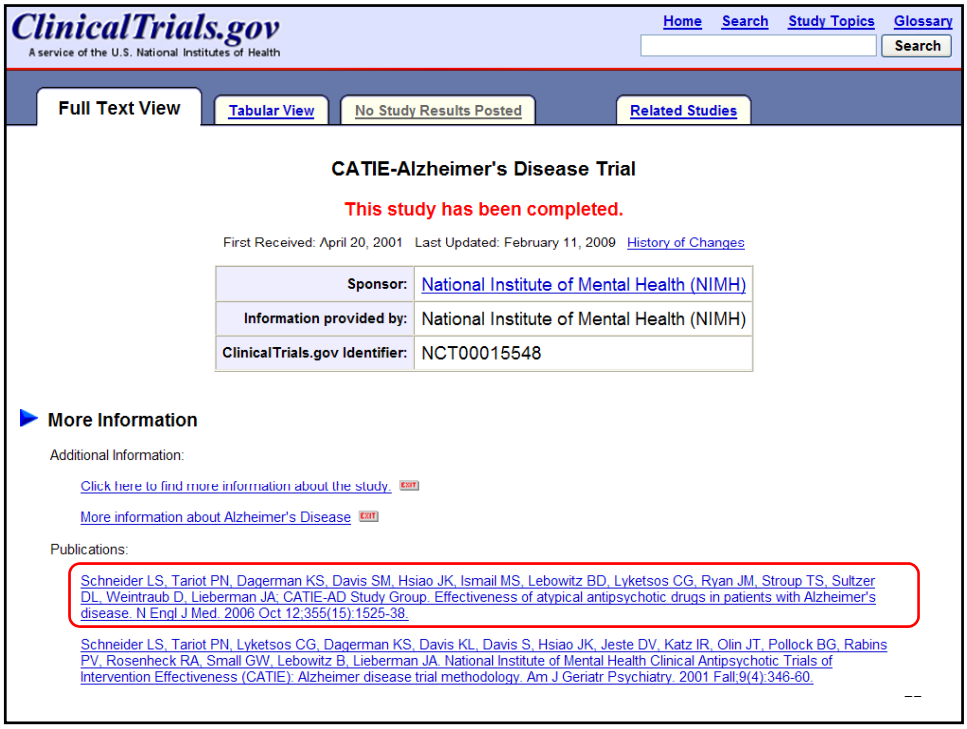
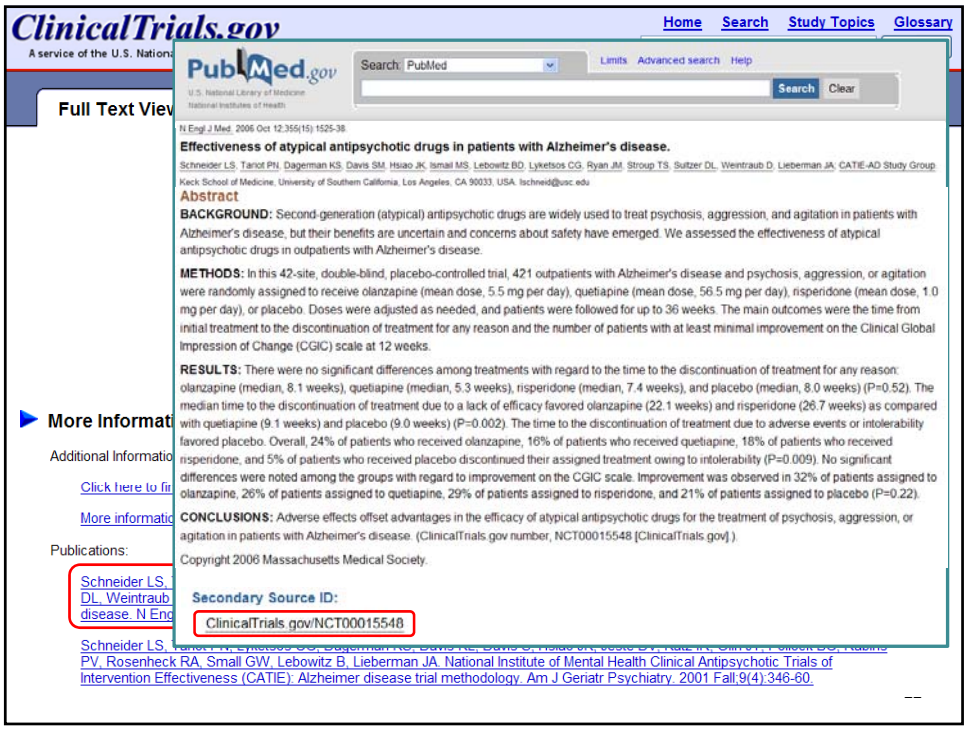
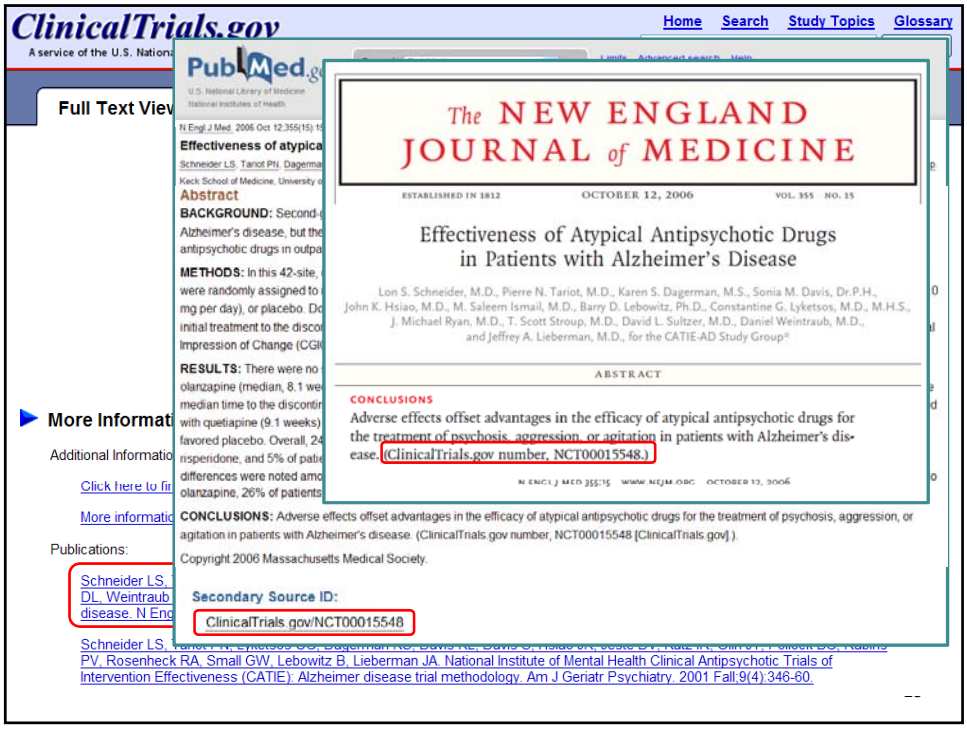
Overview of ClinicalTrials.gov







Sample Posted Record*

*Adapted from NCT00312208


ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Home Search Study Topics Glossary
Search
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
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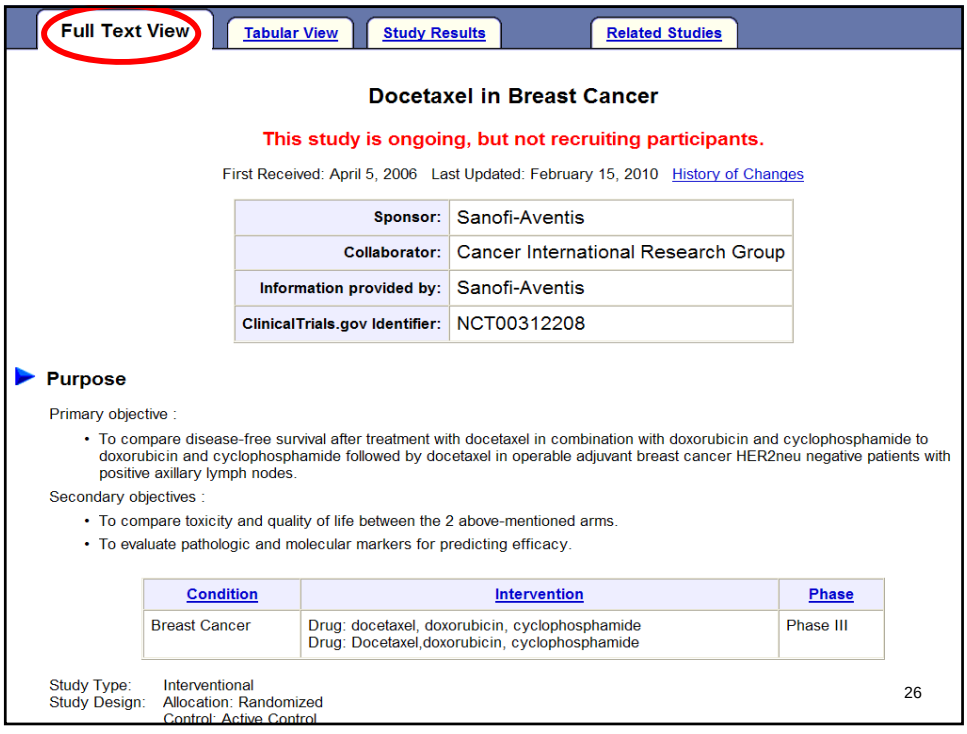
Full Text View
Tabular View
Study Results
Related Studies
Docetaxel in Breast Cancer
This study is ongoing, but not recruiting participants.
First Received: April 5, 2006 Last Updated: February 15, 2010 History of Changes
Sponsor: Sanofi-Aventis
Collaborator: Cancer International Research Group
Information 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
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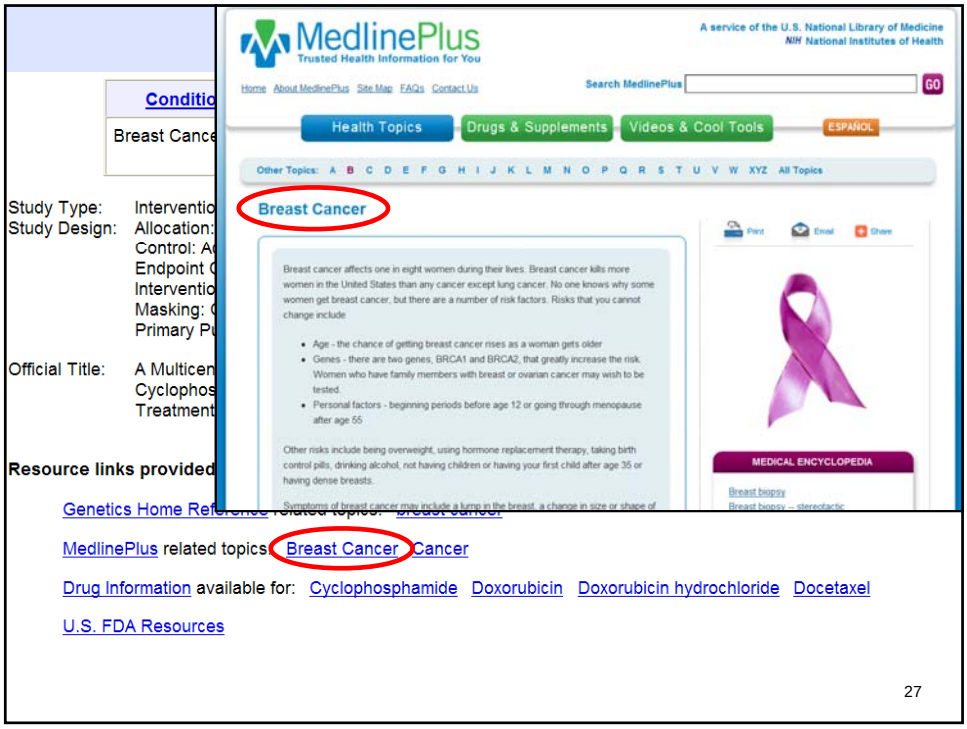
MedlinePlus
Trusted Health Information for You
A service of the U.S. National Library of Medicine
NIH National Institutes of Health
Health Topics
Drugs & Supplements
Videos & Cool Tools
ESPAÑOL
Breast Cancer
MEDICAL ENCYCLOPEDIA
Study Type:
Study Design:
Official Title:
Resource links provided
Genetics Home Reference
MedlinePlus related topics: Breast Cancer Cancer
Drug Information available for: Cyclophosphamide Doxorubicin Doxorubicin hydrochloride Docetaxel
U.S. FDA Resources
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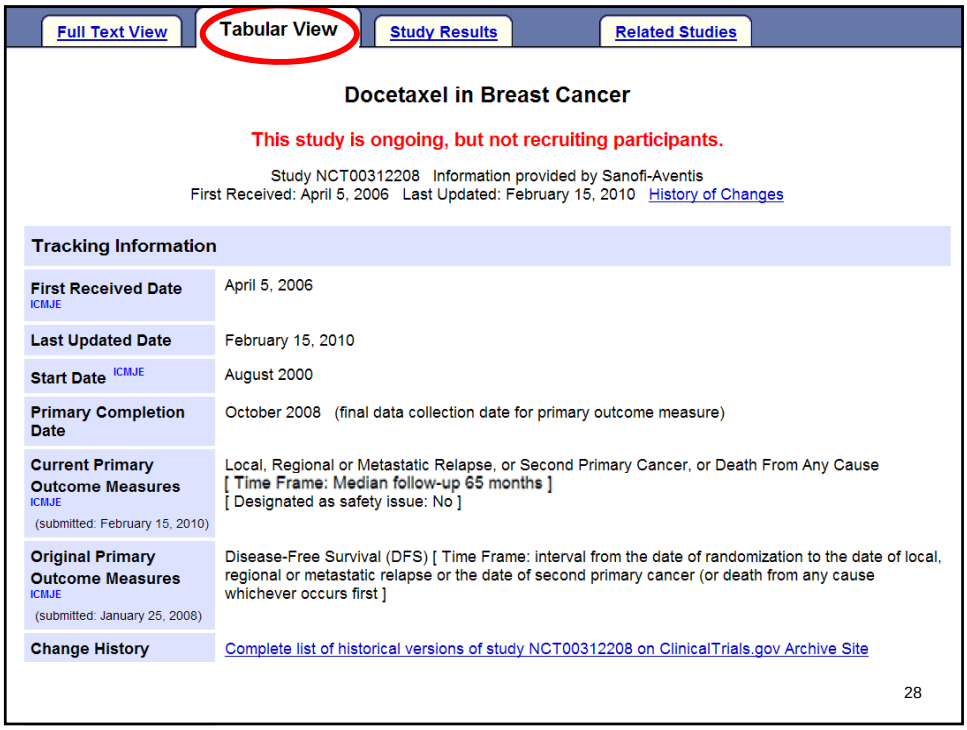
Full Text View
Tabular View
Study Results
Related Studies
Docetaxel in Breast Cancer
This study is ongoing, but not recruiting participants.
Study NCT00312208 Information provided by Sanofi-Aventis
First Received: April 5, 2006 Last Updated: February 15, 2010 History of Changes
Tracking Information
First Received Date ICMJE
April 5, 2006
Last Updated Date
February 15, 2010
Start Date ICMJE
August 2000
Primary Completion Date
October 2008 (final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE (submitted: February 15, 2010)
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 ICMJE (submitted: January 25, 2008)
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
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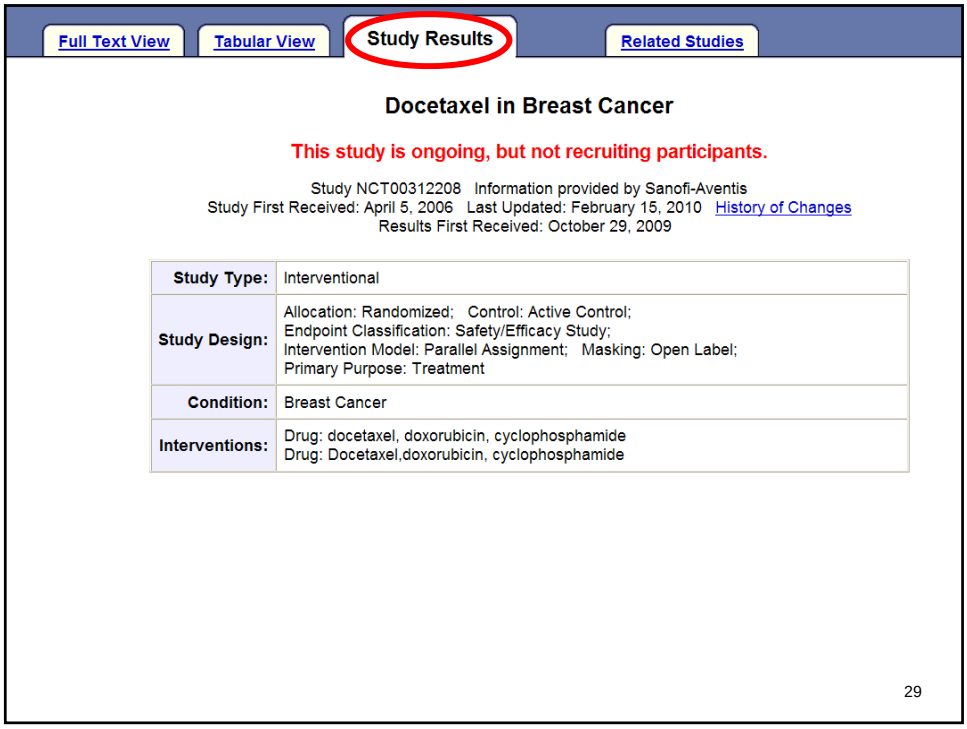

Participant Flow

"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)]

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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

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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)]

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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]			

"Default" Required Measures

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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			

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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)]

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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)]

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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)

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)

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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)]

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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

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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)]

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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

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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)]

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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.

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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

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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

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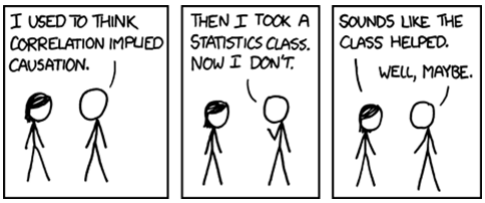
Problems Detected in Results Records

Need for Rigor and Precision



http://xkcd.com/552/

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Invalid Entry

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

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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**

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“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)*(number of pregnancies)*(4 cycles/year)/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

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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

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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)

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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

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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

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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

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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.

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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