

# ClinicalTrials.gov

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May 26, 2010



# Outline

- Rationale for clinical trial registration and results reporting
- History of ClinicalTrials.gov
- Key policies and laws
- Basics of registration and results reporting

June 2, 2004

## New York Sues Maker of Antidepressant Drug Paxil

By KENNETH N. GILPIN

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

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

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

SPECIAL ARTICLE

# Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S.,  
Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

# Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation

Kristin Rising<sup>1</sup>, Peter Bacchetti<sup>2</sup>, Lisa Bero<sup>3\*</sup>

**1** School of Medicine, University of California San Francisco, San Francisco, California, United States of America, **2** Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, United States of America, **3** Clinical Pharmacy and Health Policy, University of California San Francisco, San Francisco, California, United States of America

## Conclusions

Many trials were still not published 5 y after FDA approval. Discrepancies between the trial information reviewed by the FDA and information found in published trials tended to lead to more favorable presentations of the NDA drugs in the publications. Thus, the information that is readily available in the scientific literature to health care professionals is incomplete and potentially biased.

# CLASS study

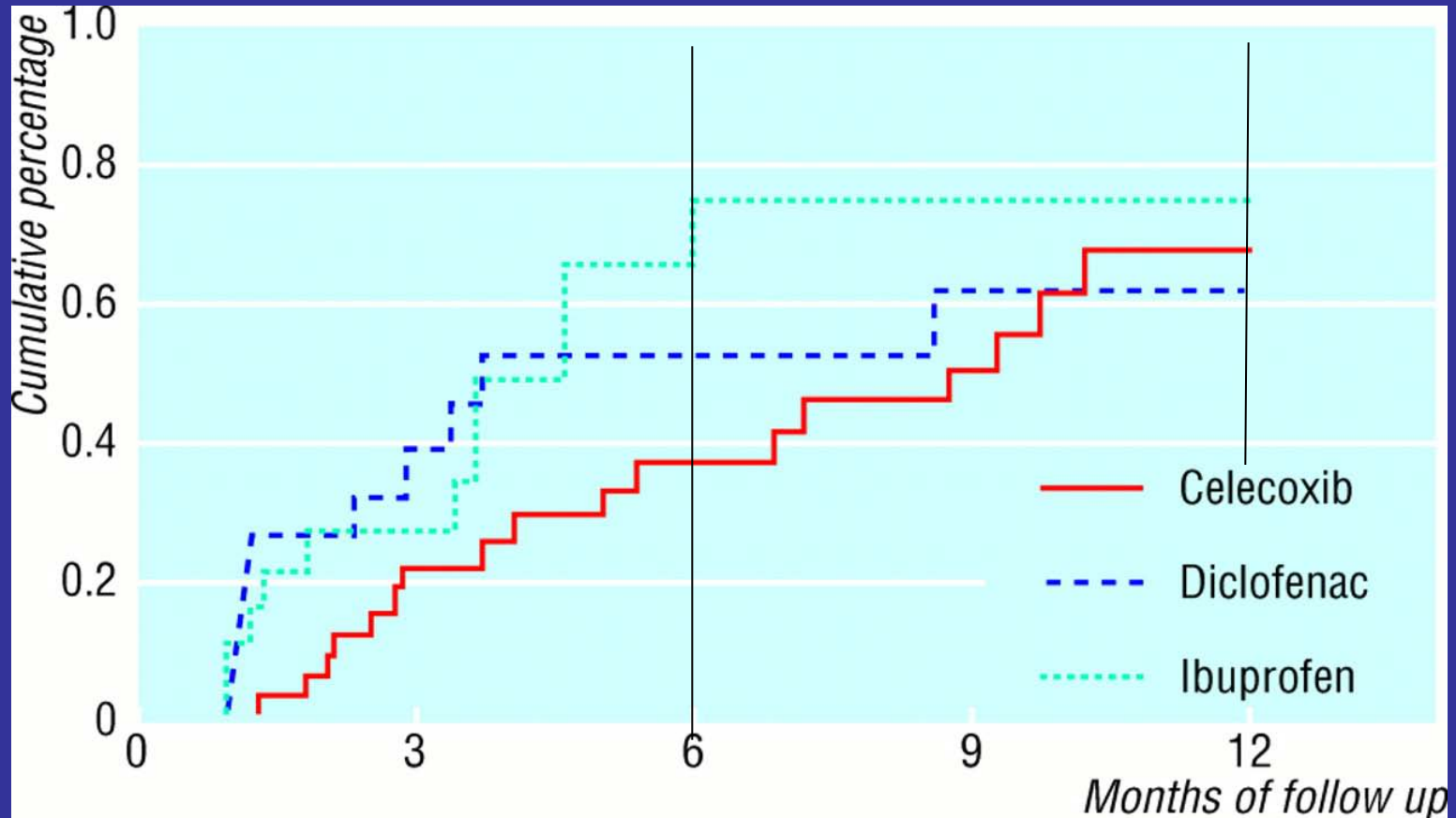


Fig 2 Kaplan-Meier estimates for ulcer complications according to traditional definition. Results are truncated after 12 months, no ulcer complications occurred after this period. Adapted from Lu 2001.

# Issues Identified with Clinical Trials

- Each step in clinical trial important
- Can never have complete oversight
- Problems have been seen at each level:
  - Design
  - Conduct
  - Analysis
  - Interpretation

# Levels of “Transparency”



# 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

# History of ClinicalTrials.gov

# 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 database

# Rate of New Registrations

- After FDAMA: 25-30 per week
- After ICMJE: 200 - 250 per week
- After FDAAA: 300 - 350 per week

# ClinicalTrials.gov Statistics

(as of 5/10/2010)

	<u>Number</u>	<u>Percent</u>
Total	89,517	100%
Type of Trial		
Observational	15,124	17%
Interventional	74,107	83%
– Drug & Biologic	53,320	
– Behavioral, Gene Transfer, Other	15,250	
– Surgical Procedure	9,180	
– Device*	5,483	
International Sites (172 countries)		
US only	41,285	46%
Non-US only	33,130	37%
US & Non-US mixed	5,780	6%
Missing	9,322	10%

# Key Policies and Laws

# ICMJE Policy

- Editorial 2004 (and updates)
- Prospective registration is a pre-requisite for publication
- What?
  - Interventional studies
  - All phases
  - All intervention types
- Where?
  - ClinicalTrials.gov or WHO Primary registry
- When?
  - Registration prior to enrollment of first participant

# FDAAA – Section 801

## Food and Drug Administration Amendments Act of 2007

- Enacted September 27, 2007
- Requires registration and results reporting
- Includes enforcement provisions
  - Notices of non-compliance
  - Civil monetary penalties up to \$10,000/day
  - Withholding of NIH grant funds
- What?
  - “Applicable Clinical Trials” (see next slide)
- Where?
  - ClinicalTrials.gov
- When?
  - Within 21 days of enrollment of first participant

# FDAAA – Key Terms

- Applicable Clinical Trials
  - Interventional trials
  - Phase 2-4; includes drug, biologic, or device
  - At least one site in U.S. or IND/IDE
  - 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

# FDAAA 801- Results

- Results of “applicable clinical trials” of FDA-*approved/cleared* medical products
- Generally, submission within 12 months of primary completion date (**final collection of data for primary outcome**)
- Delayed Submission of Results
  - Seeking initial approval
  - Seeking approval of a new use
  - Extensions for “good cause”

# Bottom Line

- Determine who is the Responsible Party
  - Sponsor or Principal Investigator
- Register prior to enrollment (or within 21 days):
  - Phase 2-4 interventional trials that include a drug, device or biologic
- 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!

# Registration

Search

Study 1 of 1 for search of: NCT00056407

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## "REDUCE" - A Clinical Research Study To Reduce The Incidence Of Prostate Cancer In Men Who Are At Increased Risk

**This study has been completed.**

First Received: March 11, 2003 Last Updated: May 6, 2010 [History of Changes](#)

<b>Sponsor:</b>	GlaxoSmithKline
<b>Information provided by:</b>	GlaxoSmithKline
<b>ClinicalTrials.gov Identifier:</b>	NCT00056407

## "REDUCE" - A Clinical Research Study To Reduce The Incidence Of Prostate Cancer In Men Who Are At Increased Risk

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<b>Sponsor:</b>	GlaxoSmithKline
<b>Information provided by:</b>	GlaxoSmithKline
<b>ClinicalTrials.gov Identifier:</b>	NCT00056407

### ► Purpose

This 4-year study will compare how safe and effective an oral investigational medicine is (compared to placebo) in preventing the development of prostate cancer in men that are defined by the study entrance criteria as being at an increased risk for prostate cancer. Study visits to the clinic will occur every 6 months for up to 4 years (10 clinic visits), and a prostate biopsy will be performed at 2 and 4 years of treatment.

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Prostate Cancer	Drug: Placebo Drug: Dutasteride	Phase III

Study Type: Interventional  
 Study Design: Allocation: Randomized  
 Endpoint Classification: Safety/Efficacy Study  
 Intervention Model: Parallel Assignment  
 Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)  
 Primary Purpose: Prevention

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## Prostate Cancer

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Study Type: Inte

Study Design: Allc

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Official Title: A R

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Resource links pr

The prostate is the gland below a man's bladder that produces fluid for semen. Prostate cancer is the third most common cause of death from cancer in men of all ages. It is rare in men younger than 40.

Levels of a substance called prostate specific antigen (PSA) is often high in men with prostate cancer. However, PSA can also be high with other [prostate conditions](#). Since the PSA test became common, most prostate cancers are found before they cause symptoms. Symptoms of prostate cancer may include

- Problems passing urine, such as pain, difficulty starting or stopping the stream, or dribbling
- Low back pain
- Pain with ejaculation

Prostate cancer treatment often depends on the stage of the cancer. How fast the cancer grows and how different it is from surrounding tissue helps determine the stage. Treatment may include surgery, radiation therapy, chemotherapy or control of hormones that affect the cancer.



### Encyclopedia

- [Pelvic CT scan](#)
- [Pelvis MRI scan](#)
- [Prostate brachytherapy](#)
- [Prostate brachytherapy -](#)

MedlinePlus related topics: [Cancer](#) [Prostate Cancer](#)

Drug Information available for: [Dutasteride](#)

[U.S. FDA Resources](#)



ORIGINAL ARTICLE

Previous

Volume 362:1192-1202

April 1, 2010

Number 13

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Effect of Dutasteride on the Risk of Prostate Cancer

Gerald L. Andriole, M.D., David G. Bostwick, M.D., Otis W. Brawley, M.D., Leonard G. Gomella, M.D., Michael Marberger, M.D., Francesco Montorsi, M.D., Curtis A. Pettaway, M.D., Teuvo L. Tammela, M.D., Claudio Teloken, M.D., Ph.D., Donald J. Tindall, Ph.D., Matthew C. Somerville, M.S., Timothy H. Wilson, M.S., Ivy L. Fowler, B.S.N., Roger S. Rittmaster, M.D., for the REDUCE Study Group

Effect of Dutasteride on the Risk of Prostate Cancer

Andriole G  
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Collabo  
Division of U  
Comment

N Engl J Med

Abstract  
BACKGR  
cancer, as  
multicente

**Background** We conducted a study to determine whether dutasteride reduces the risk of incident prostate cancer, as detected on biopsy, among men who are at increased risk for the disease.

**Methods** In this 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, we compared dutasteride, at a dose of 0.5 mg daily, with placebo. Men were eligible for inclusion in the study if they were 50 to 75 years of age, had a prostate-specific antigen (PSA) level of 2.5 to 10.0 ng per milliliter, and had had one negative prostate biopsy (6 to 12 cores) within 6 months before enrollment. Subjects underwent a 10-core transrectal ultrasound-guided biopsy at 2 and 4 years.

**Results** Among 6729 men who underwent a biopsy or prostate surgery, cancer was detected in 659 of the 3305 men in the dutasteride group, as compared with 858 of the 3424 men in the placebo group, representing a relative risk reduction with dutasteride of 22.8% (95% confidence interval, 15.2 to 29.8) over the 4-year study period (P<0.001). Overall, in years 1 through 4, among the 6706 men who underwent a needle biopsy, there were 220 tumors with a Gleason score of 7 to 10 (3.1% vs. 3.9% in the placebo group; P=0.003). Dutasteride therapy, as compared with placebo, resulted in a reduction in the rate of acute urinary retention (1.6% vs. 6.7%, a 77.3% relative reduction). The incidence of adverse events was similar to that in studies of dutasteride therapy for benign prostatic hyperplasia, except that in our study, as compared with previous studies, the relative incidence of the composite category of cardiac failure was higher in the dutasteride group than in the placebo group (0.7% [30 men] vs. 0.4% [16 men]; P=0.03).

**Conclusions** Over the course of the 4-year study period, dutasteride reduced the risk of incident prostate cancer detected on biopsy and improved the outcomes related to benign prostatic hyperplasia. (ClinicalTrials.gov number, NCT00056407 [ClinicalTrials.gov].)

May 6, 2010

Canada: Health Canada; Sweden: Medical Products Agency; United States: Food and Drug Administration

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- Editorial by Walsh, P. C.

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More Information

No publications provided

Additional publication Identifier (NCT ID):

Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, Pettaway CA, Tammela TL, Teloken C, Tindall DJ, Somerville M, Wilson T, Fowler I, Rittmaster R. Effect of Dutasteride on the Risk of Prostate Cancer. N Engl J Med. 2010 Apr 1;362(13):1192-202. doi: 10.1056/NEJMoa0911281. Epub 2010 Mar 22.

Responsible Party:

ClinicalTrials.gov Identifier:

Other Study ID Numbers:

Study First Received:

Results First Received:

Last Updated:

Health Authority:

# Protocol Information

- Descriptive Information
  - Study Type, Phase, Design, Outcomes, # Subjects, 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)

## ClinicalTrials.gov Protocol Data Element Definitions (DRAFT)

August 20, 2008

- 
- \* Required by ClinicalTrials.gov
  - FDAAA** Required to comply with US Public Law 110-85, Section 801
  - (FDAAA)** May be required to comply with US Public Law 110-85, Section 801
- 

### 1. Titles and Background Information

#### **Organization's Unique Protocol ID** \* **FDAAA**

Definition: Unique identification assigned to the protocol by the sponsoring organization, usually an accession number or a variation of a grant number. Multiple studies conducted under the same grant must each have a unique number.

Examples:

ABT-1233-RV

Merck-023

ACTG 021

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## "REDUCE" - A Clinical Research Study To Reduce The Incidence Of Prostate Cancer In Men Who Are At Increased Risk

**This study has been completed.**

Study NCT00056407 Information provided by GlaxoSmithKline  
First Received: March 11, 2003 Last Updated: May 6, 2010 [History of Changes](#)

### Tracking Information

**First Received Date**

March 11, 2003

[ICMJE](#)**Last Updated Date**

May 6, 2010

**Start Date** [ICMJE](#)

March 2003

**Primary Completion Date**

January 2009 (final data collection date for primary outcome measure)

**Current Primary Outcome Measures**[ICMJE](#)

(submitted: April 15, 2010)

- Number of Participants With Biopsy-detectable Prostate Cancer at Years 2 and 4 (Crude Rate Approach) [ Time Frame: Years 1-2, Years 3-4, and Overall ]  
[ Designated as safety issue: No ]

Study biopsies consisted of 10 biopsy samples (cores) in a pre-defined pattern. Biopsies were read at the central pathology laboratory (CPL, which processed the majority, 94%, of biopsies). Biopsy cases that were positive for prostate cancer or precancerous lesions (high-grade prostatic intraepithelial neoplasia[HGPIN] or typical small acinar proliferation [ASAP]) and prostate surgeries were reviewed by the lead pathologist.

# Basic Results Database

# Current Status – “Basic Results”

(as of 5/13/10)

- Launched in September 2008
- 2,614 Results Records submitted
  - Industry: 1,985 records from 237 data providers (~8 records/provider)
  - Other: 629 records from 322 data providers (~2 records/provider)
- Rate of submission continues to increase
  - 90 records per week now
  - Anticipate about 150 per week

# Results Information

- Participant Flow
- Baseline and Demographic Characteristics
- Outcome Measures
- Adverse Events (summary data)
- Other Information
  - “Certain Agreements” related to *Restrictions on Results Disclosure*
  - Overall Limitations and Caveats
  - Results Point of Contact

# Basic Results: Data Elements

<http://prsinfo.clinicaltrials.gov>

## ClinicalTrials.gov "Basic Results" Data Element Definitions (DRAFT)

September 28, 2009

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- \* Required by ClinicalTrials.gov
  - [\*] Conditionally required by ClinicalTrials.gov
  - (FDAAA) May be required to comply with US Public Law 110-85, Section 801
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# Sample Posted Results

Study 1 of 4618 for search of: REDUCE

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**Study Results**

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## "REDUCE" - A Clinical Research Study To Reduce The Incidence Of Prostate Cancer In Men Who Are At Increased Risk

**This study has been completed.**

Study NCT00056407 Information provided by GlaxoSmithKline

Study First Received: March 11, 2003 Last Updated: May 6, 2010 [History of Changes](#)

Results First Received: February 1, 2010

<b>Study Type:</b>	Interventional
<b>Study Design:</b>	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Prevention
<b>Condition:</b>	Prostate Cancer
<b>Interventions:</b>	Drug: Placebo Drug: Dutasteride

# 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)]

8231 Patients underwent randomization to double-blind phase (safety population)  
 4105 Were in dutasteride group  
 4126 Were in placebo group

109 (1.3%) Were excluded  
 56 Were in dutasteride group  
 53 Were in placebo group  
 20 Did not receive drug  
 10 Were in dutasteride group  
 10 Were in placebo group  
 53 Had positive baseline biopsy  
 27 Were in dutasteride group  
 26 Were in placebo group  
 38 Had no baseline biopsy review  
 21 Were in dutasteride group  
 17 Were in placebo group

8122 (98.7%) Were included  
 4049 Were in dutasteride group  
 4073 Were in placebo group

1393 (17.2%) Had no biopsy  
 744 Were in dutasteride group  
 649 Were in placebo group

6608 (98.7%) Had biopsy  
 3244 Were in dutasteride group  
 3364 Were in placebo group

### Participant Flow: Overall Study

	Placebo	Dutasteride 0.5 mg
<b>STARTED</b>	<b>4126</b>	<b>4105</b>
<b>COMPLETED</b>	<b>2915</b>	<b>2912</b>
<b>NOT COMPLETED</b>	<b>1211</b>	<b>1193</b>
<b>Adverse Event</b>	<b>282</b>	<b>364</b>
<b>Withdrawal by Subject</b>	<b>377</b>	<b>361</b>
<b>Lost to Follow-up</b>	<b>123</b>	<b>113</b>
<b>Protocol Violation</b>	<b>104</b>	<b>95</b>
<b>Diagnosed with Prostate Cancer</b>	<b>202</b>	<b>166</b>
<b>Listed as "Other" on Case Report Form</b>	<b>98</b>	<b>60</b>
<b>Missing</b>	<b>25</b>	<b>34</b>

# 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)]

**Table 1. Baseline Characteristics of the Study Participants.\***

Characteristic	Total (N= 8231)	Dutasteride (N= 4105)	Placebo (N= 4126)
----------------	--------------------	--------------------------	----------------------

Age — yr
Mean
Range
Race or ethnic group — no. (%) <sup>†</sup>
White
Black
Asian
American Hispanic
Other
Body-mass index <sup>‡</sup>
Geographic region — no. (%)
Europe
Canada, United States, and Puerto Rico
Other
Family history of prostate cancer — no. (%)
Prostate-specific antigen
Total — ng/ml
Free — %
Prostate volume — ml
PSA density <sup>§</sup>
Cores at baseline biopsy — no.
International Prostate Symptom Score <sup>¶</sup>

**Baseline Measures**

	Placebo	Dutasteride 0.5 mg	Total
<b>Number of Participants</b> [units: participants]	<b>4126</b>	<b>4105</b>	<b>8231</b>
<b>Age</b> [units: years] Mean ± Standard Deviation	<b>62.7 ± 6.08</b>	<b>62.8 ± 6.04</b>	<b>62.8 ± 6.06</b>
<b>Gender</b> [units: participants]			
<b>Female</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Male</b>	<b>4126</b>	<b>4105</b>	<b>8231</b>
<b>Race/Ethnicity, Customized</b> [units: participants]			
<b>White</b>	<b>3747</b>	<b>3744</b>	<b>7491</b>
<b>Black</b>	<b>99</b>	<b>91</b>	<b>190</b>
<b>Asian</b>	<b>67</b>	<b>67</b>	<b>134</b>
<b>American Hispanic</b>	<b>173</b>	<b>160</b>	<b>333</b>
<b>Other</b>	<b>39</b>	<b>43</b>	<b>82</b>
<b>Missing</b>	<b>1</b>	<b>0</b>	<b>1</b>

# Outcome Measure

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

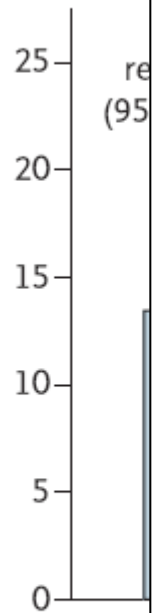
[Sec. 282(j)(3)(C)(ii)]

# 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)]

Proportion of Men with Prostate Cancer Detected (%)



**Figure 2.** Proportion of Men with Prostate Cancer Detected (%) by Treatment Group.

### Measured Values

	Placebo	Dutasteride 0.5 mg
<b>Number of Participants Analyzed</b> [units: participants]	<b>4073</b>	<b>4049</b>
<b>Number of Participants With Biopsy-detectable Prostate Cancer at Years 2 and 4 (Crude Rate Approach)</b> [units: participants]		
<b>Years 1- 2, n=4073, 4049</b>	<b>578</b>	<b>435</b>
<b>Years 3- 4, n=2815, 2844</b>	<b>280</b>	<b>224</b>
<b>Overall, n=4073, 4049</b>	<b>858</b>	<b>659</b>

### Statistical Analysis 1 for Number of Participants With Biopsy-detectable Prostate Cancer at Years 2 and 4 (Crude Rate Approach)

<b>Groups</b> <sup>[1]</sup>	All groups
<b>Method</b> <sup>[2]</sup>	Mantel-Cox
<b>P Value</b> <sup>[3]</sup>	<0.0001
<b>Relative Risk Reduction</b> <sup>[4]</sup>	23.3
<b>95% Confidence Interval</b>	( 15.6 to 30.3 )

# 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)]

**Serious Adverse Events**

**Table 4. Incidence**

		Placebo	Dutasteride 0.5 mg
<b>Event</b>	<b>Total, serious adverse events</b>		
	<b># participants affected / at risk</b>	<b>837/4126 (20.29%)</b>	<b>748/4105 (18.22%)</b>
	<b>Blood and lymphatic system disorders</b>		
Any adverse event	<b>Iron deficiency anaemia †A</b> # participants affected / at risk	<b>3/4126 (0.07%)</b>	<b>2/4105 (0.05%)</b>
Any serious adverse event	<b>Lymphadenopathy †A</b> # participants affected / at risk	<b>1/4126 (0.02%)</b>	<b>3/4105 (0.07%)</b>
Drug-related adverse event	<b>Thrombocytopenia †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>4/4105 (0.10%)</b>
Any	<b>Anaemia †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>2/4105 (0.05%)</b>
Leading to permanent discontinuation of treatment	<b>Febrile neutropenia †A</b> # participants affected / at risk	<b>1/4126 (0.02%)</b>	<b>1/4105 (0.02%)</b>
Occurring in ≥1 serious adverse event, either study-related or unrelated	<b>Leukopenia †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>2/4105 (0.05%)</b>
Decreased libido	<b>Microcytic anaemia †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>2/4105 (0.05%)</b>
Loss of libido	<b>Splenomegaly †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>2/4105 (0.05%)</b>
Erectile dysfunction	<b>Leukocytosis †A</b> # participants affected / at risk	<b>1/4126 (0.02%)</b>	<b>0/4105 (0.00%)</b>
Decreased sexual desire	<b>Splenic haemorrhage †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>1/4105 (0.02%)</b>
Gynecomastia	<b>Autoimmune thrombocytopenia †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>1/4105 (0.02%)</b>
Death§	<b>Blood disorder †A</b> # participants affected / at risk	<b>0/4126 (0.00%)</b>	<b>1/4105 (0.02%)</b>

# 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)]

**Table 4.** Inc

**Other Adverse Events**

Event  
Any adverse  
Any serious  
Drug-relate  
Any  
Leading  
Occurri  
Dec  
Loss  
Erec  
Dec  
Gyn  
Death§

	Placebo	Dutasteride 0.5 mg
<b>Total, other (not including serious) adverse events</b> # participants affected / at risk	<b>1151/4126</b>	<b>1296/4105</b>
<b>Cardiac disorders</b>		
<b>Hypertension †<sup>A</sup></b> # participants affected / at risk	<b>321/4126 (7.78%)</b>	<b>349/4105 (8.50%)</b>
<b>Infections and infestations</b>		
<b>Nasopharyngitis †<sup>A</sup></b> # participants affected / at risk	<b>288/4126 (6.98%)</b>	<b>313/4105 (7.62%)</b>
<b>Influenza †<sup>A</sup></b> # participants affected / at risk	<b>212/4126 (5.14%)</b>	<b>204/4105 (4.97%)</b>
<b>Musculoskeletal and connective tissue disorders</b>		
<b>Back pain †<sup>A</sup></b> # participants affected / at risk	<b>245/4126 (5.94%)</b>	<b>261/4105 (6.36%)</b>
<b>Reproductive system and breast disorders</b>		
<b>Erectile dysfunction †<sup>A</sup></b> # participants affected / at risk	<b>363/4126 (8.80%)</b>	<b>494/4105 (12.03%)</b>

† Indicates events were collected by systematic assessment.

<sup>A</sup> Term from vocabulary, MedDRA

# Issues in Reporting Results

# ICMJE

“...will not consider results posted in the same primary clinical trials register in which the initial registration resides as previous publication if the results are presented in the form of a brief, structured (<500 words) abstract or table.”

# 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)

# Protocol and Results Review

- Protocol and results must be clear and informative
- Review focuses on:
  - Logic and internal consistency
  - Apparent validity
  - Meaningful entries
  - Formatting
- Note: Review is NOT “peer review”

# Review System Upgrades

- Automated validation during data entry
  - Notes, warnings, errors
- Review comments integrated into PRS
- Online help text / links to user documents
  - Helpful hints
  - Avoiding Common errors
  - Detailed Review Items
- Individual consultations as needed

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

## "Basic Results" Database

- [Adverse Event Reporting](#) - information on the requirements for reporting adverse events
- [Guide to Results Data Entry - \(CHEST, 2009 Jul;136\(1\):295-303\)](#) - article includes summary results reporting requirements, brief descriptions of the results database modules, and suggestions for preparing results submissions
- [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, including adverse events, via the PRS.
- [Detailed Review Items \(pdf\) \(DRAFT\)](#) - describes items evaluated by ClinicalTrials.gov after results have been submitted.
- [Basic Results Provisions \(pdf\)](#) - 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

# Detailed Review Items

DRAFT

09-04-09

## ClinicalTrials.gov Review of Results Submissions

### **Background**

Protocol and results information must be clear and informative. Prior to submission of results, a record must have summary protocol information and an assigned NCT Number (ClinicalTrials.gov unique identifier). ClinicalTrials.gov reviews protocol and results information for apparent validity, meaningful entries, logic and internal consistency, and formatting. The review focuses on assessing whether the entered data could be understood by a reader of the medical literature who is not already familiar with the study.

This document is intended to assist data providers in preparing results records by providing an overview of ClinicalTrials.gov review criteria. This document is not comprehensive. It is the responsibility of the data provider to ensure that records are consistent with these criteria. The public posting of a results record by ClinicalTrials.gov does not necessarily mean that all of these criteria have been met. At times, ClinicalTrials.gov may note problems and request revisions after results have been posted publicly. Additional explanatory user documents are also available at <http://prsinfo.clinicaltrials.gov/fdaaa.html>.

### **Results Review Criteria**

#### **General**

- Records are in English (with possible exception for the Official Title).
- Acronyms and abbreviations are spelled out fully (with acronym in parentheses) at least the first time they are used in the Protocol and Results Sections.
- No spelling errors exist. Note: The Spelling Tool on the “View Protocol Record” page may be used to identify possible spelling errors.
- No formatting problems exist, including any unreadable characters or symbols.
  - Unicode, UTF-8 format, is the standard for ClinicalTrials.gov

# Unclear Outcome Measure

<b>Measure Name</b>	Time to Disease-Free Survival
<b>Measure Description</b>	Time from date of treatment to date of survival
<b>Time Frame</b>	5 years

	<b>Drug A</b>	<b>Drug B</b>
<b>Number of Participants Analyzed</b> [units: participants]	648	645
<b>Time to Disease-Free Survival</b> [units: participants]	246	277

# Invalid Data

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

# Informative Entry

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

	<b>DR-1011</b>
<b>Number of Participants Analyzed</b>	1735
<b>Pregnancy Rate (Pearl Index)</b> [units: Pregnancies per 100 woman years exposure]	2.74

# Informative Entry

<b>Measure Name</b>	Time to Progressive Disease
<b>Measure Description</b>	Time from study enrollment to the first date of disease progression. Time to disease progression was censored at the date of death if death was due to other cause.
<b>Time Frame</b>	Every other 21 day cycle (6-8 cycles) and every 3 months during follow-up

	<b>Drug X</b>
<b>Number of Participants Analyzed</b>	50
<b>Time to Progressive Disease</b> [units: weeks]	45.1
Median ( 95% Confidence Interval )	( 37.9 to 56.9 )

# Lessons Learned from Early Submissions of Basic Results

- Data Providers must be able to understand the study design and data analysis
  - Typically, the investigator and a statistician will need to be involved

# Next Steps

- September 27, 2010: Expansion by Rulemaking

# Key Issues in Expansion

- Expand results reporting to trials of unapproved products?
- Include narrative summaries? Can it be done w/out being promotional and misleading?
  - Technical
  - Lay Language
- Data Quality Verification
  - Process (e.g., Pilot Quality Control Project)
  - External Sources
- Full protocol versus extract “necessary to help evaluate the results”

# Resources

# Additional Information

(at <http://prsinfo.clinicaltrials.gov/fdaaa.html>)

- "Basic Results" Data Element Definitions
- Helpful Hints - tips on entering results data, including examples of common study models (e.g., crossover design)
- Detailed Review Items - describes items evaluated by ClinicalTrials.gov staff
- Common Errors - overview of common types of errors identified in submitted records with "basic results"

# Additional Background

- 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.

# 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](mailto:register@clinicaltrials.gov)

# Questions?



*National Library of Medicine & Lister Hill Center for Biomedical Communications  
Bethesda, MD*

# Using ClinicalTrials.gov

ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals. [Read more...](#)

## Resources:

[Understanding Clinical Trials](#)

[What's New](#)

[Glossary](#)

## [Search for Clinical Trials](#)

Find trials for a specific medical condition or other criteria in the ClinicalTrials.gov registry. ClinicalTrials.gov currently has **90,137 trials** with locations in **172 countries**.

## Study Topics:

[List studies by Condition](#)

[List studies by Drug Intervention](#)

[List studies by Sponsor](#)

[List studies by Location](#)

## ▶ [Investigator Instructions](#)

Get instructions for clinical trial investigators/sponsors about how to register trials in ClinicalTrials.gov. Learn about mandatory registration and results reporting requirements and US Public Law 110-85 (FDAAA).

## ▶ [Background Information](#)

Learn about clinical trials and how to use ClinicalTrials.gov, or access other consumer health information from the US National Institutes of Health.



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[Studies on Map](#)

Enter a word or phrase, such as the name of a medical condition or intervention.

**Example: Heart Attack AND Los Angeles**

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### Search Tips:

Use AND (all upper case) to search for multiple terms. For example:

prostate cancer AND radiation

heart disease AND stroke AND California

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[Recruitment:](#) All Studies

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**Targeted Search:**

[Conditions:](#) heart

[Interventions:](#)

[Outcome Measures:](#)

[Lead Sponsors:](#)

[Sponsors:](#)

[Study IDs:](#)

Exact Match

Exact Match

**Locations:**

[State 1:](#) United States, Wisconsin

[Country 1:](#) --- Optional ---

[State 2:](#) --- Optional ---

[Country 2:](#) --- Optional ---

[State 3:](#) --- Optional ---

[Country 3:](#) --- Optional ---

[Location Terms:](#) Milwaukee AND Aurora

Search

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[Search Details](#)

Found 17 studies with search of: heart | United States, Wisconsin | Milwaukee AND Aurora

[Hide studies that are not seeking new volunteers.](#)

[+ Display Options](#)

Rank	Status	Study
1	Completed	<p><a href="#">Exercise Training Program to Improve Clinical Outcomes in Individuals With Congestive Heart Failure</a></p> <p>Conditions: Cardiovascular Diseases; Heart Diseases; Heart Failure, Congestive</p> <p>Intervention: Behavioral: Supervised Exercise Training Program</p>
2	Active, not recruiting	<p><a href="#">XIENCE V® USA Dual Antiplatelet Therapy (DAPT) Cohort</a></p> <p>Conditions: Chronic Coronary Occlusion; Vascular Disease; Myocardial Ischemia; Coronary Artery Stenosis; Coronary Disease; Coronary Artery Disease; Coronary Restenosis</p> <p>Intervention: Drug: Thienopyridine (clopidogrel or prasugrel)</p>
3	Recruiting	<p><a href="#">Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy</a></p> <p>Condition: Advanced Heart Failure</p> <p>Intervention: Device: HeartPOD™ System or Promote® LAP System</p>
4	Recruiting	<p><a href="#">Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure</a></p> <p>Condition: Advanced Heart Failure</p> <p>Intervention: Device: Left Ventricular Assist Device (HeartWare® LVAD)</p>

Found 17 studies with search of: heart | United States, Wisconsin | Milwaukee AND Aurora

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Display Options - choose fields to display in search results below

- |   |   |  |  |  |
|---|---|--|--|--|
| <input checked="" type="checkbox"/> Condition | <input checked="" type="checkbox"/> Intervention    | <input checked="" type="checkbox"/> Sponsor  | <input type="checkbox"/> Gender                  | <input type="checkbox"/> Age Group       |
| <input type="checkbox"/> Phase                | <input checked="" type="checkbox"/> Number Enrolled | <input type="checkbox"/> Funded By           | <input type="checkbox"/> Study Type              | <input type="checkbox"/> Study Design    |
| <input type="checkbox"/> NCT ID               | <input type="checkbox"/> Other IDs                  | <input type="checkbox"/> First Received Date | <input type="checkbox"/> Start Date              | <input type="checkbox"/> Completion Date |
| <input type="checkbox"/> Last Updated Date    | <input type="checkbox"/> Last Verified Date         | <input type="checkbox"/> Acronym             | <input type="checkbox"/> Primary Completion Date | <input type="checkbox"/> Outcome Measure |

Rank	Status	Study
1	Completed	<p><a href="#">Exercise Training Program to Improve Clinical Outcomes in Individuals With Congestive Heart Failure</a></p> <p>Conditions: Cardiovascular Diseases; Heart Diseases; Heart Failure, Congestive</p> <p>Intervention: Behavioral: Supervised Exercise Training Program</p> <p>Sponsor: National Heart, Lung, and Blood Institute (NHLBI)</p> <p>Number Enrolled: 2331</p>
2	Active, not recruiting	<p><a href="#">XIENCE V® USA Dual Antiplatelet Therapy (DAPT) Cohort</a></p> <p>Conditions: Chronic Coronary Occlusion; Vascular Disease; Myocardial Ischemia; Coronary Artery Stenosis; Coronary Disease; Coronary Artery Disease; Coronary Restenosis</p> <p>Intervention: Drug: Thienopyridine (clopidogrel or prasugrel)</p> <p>Sponsors: Abbott Vascular; Harvard Clinical Research Institute; Bristol-Myers Squibb; Daiichi Sankyo Inc.; Eli Lilly and Company</p> <p>Number Enrolled: 1524</p>
3	Recruiting	<p><a href="#">Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy</a></p> <p>Condition: Advanced Heart Failure</p> <p>Intervention: Device: HeartPOD™ System or Promote® LAP System</p> <p>Sponsor: St. Jude Medical</p> <p>Number Enrolled: 730</p>
4	Recruiting	<p><a href="#">Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure</a></p> <p>Condition: Advanced Heart Failure</p> <p>Intervention: Device: Left Ventricular Assist Device (HeartWare® LVAD)</p> <p>Sponsor: HeartWare, Inc.</p> <p>Number Enrolled: 150</p>

Search

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## Categorize All Studies in ClinicalTrials.gov

### Select a Main Category

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#### Rare Diseases

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#### Drug Interventions

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#### Locations

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## Categorize All Studies in ClinicalTrials.gov

**[Main Category:](#) Drug Interventions By Category**

**[Drug Intervention Category:](#) Anti-Infective Agents**

### Search for Drug Intervention

Click on a link to search for the Drug Intervention. Use the back button to return to this page to try another Drug Intervention.

[Abacavir](#) 130 studies

[Abelcet](#) 81 studies

[Acetylcysteine](#) 126 studies

[Acyclovir](#) 106 studies

[Adefovir](#) 83 studies

[Adefovir dipivoxil](#) 83 studies

[AL 721](#) 1 study

[Alatrofloxacin](#) 1 study

[Albendazole](#) 36 studies

[Aldesleukin](#) 278 studies

[Allicin](#) 4 studies

[Alovudine](#) 12 studies

[Amantadine](#) 39 studies

[Amikacin](#) 19 studies

[Ammonium trichloro\(dioxoethylene-O,O'\)-tellurate](#) 9 studies

[Amodiaquine](#) 62 studies

List Results

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[Search Details](#)

Found **101 studies with search of: "Vancomycin"**

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Rank	Status	Study
1	Completed	<a href="#">Vancomycin vs. Vancomycin Plus Gentamycin in Treatment of MRSA Infection</a> Condition: Staphylococcus Aureus Interventions: Drug: Vancomycin; Drug: Vancomycin plus Gentamicin; Drug: Vancomycin plus Rifampin; Drug: Vancomycin plus Gentamicin plus Rifampin
2	Not yet recruiting	<a href="#">Evaluating the Use of Large-dose, Extended Interval Vancomycin Intravenous Administration for Skin and Soft Tissue Infections</a> Condition: Skin and Soft Tissue Infections Intervention: Drug: vancomycin
3	Withdrawn	<a href="#">Extended Treatment With Vancomycin for Clostridium Difficile Colitis</a> Condition: Clostridium Difficile Colitis Interventions: Drug: Standard Vancomycin; Drug: Extended Vancomycin