Everything You Always Wanted to Know About ClinicalTrials.gov

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Director, ClinicalTrials.gov
November 2015

Overview

Registry and Results Database

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
  - Issued for public comment in November 2014
    - Notice of Proposed Rulemaking for Implementing FDAAA 801
    - Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

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* Food and Drug Administration Modernization Act of 1997

† Food and Drug Administration Amendments Act of 2007

Definitions

- **Registration**: “the process for making key summary information about interventional studies using human volunteers accessible to the public via a web-based system, from study initiation to completion”
- **Results Reporting**: “making summary information about study results available in a structured, publicly accessible web-based results database”

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

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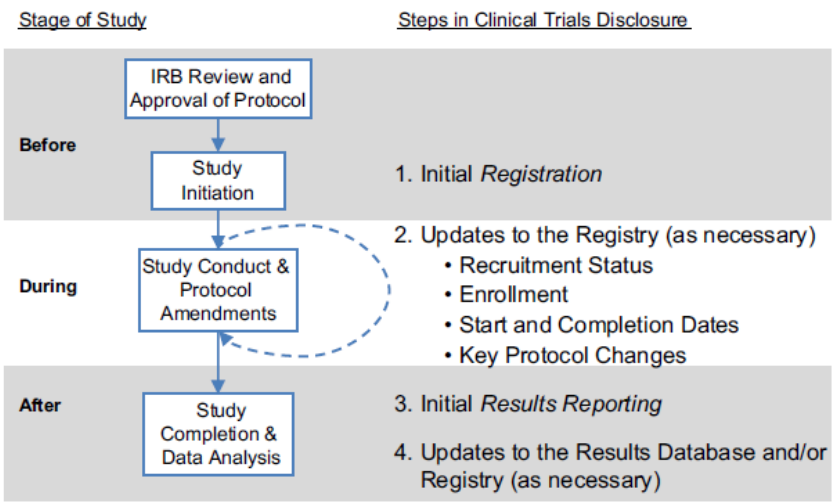
Registry Record

- Key Protocol Details
  - Intervention(s) & Outcome measure(s)
  - Eligibility Details
- Recruitment Information
- Administrative Info (includes Key Dates)
- Expected to be corrected or updated throughout the trial's life cycle



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Archival Data: Tracking Changes in the Record

- Each record is expected to be corrected or updated throughout the trial's life cycle, and all changes are tracked on a public archive site that is accessible from each record (through a "History of Changes" link).
- Tabular View
  - Current Outcome Measures
  - Original (First Registered) Outcome Measures

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Zarin et al. *N Engl J Med* 2011; 364:852-60.

The Results Database

- FDAAA enacted in September 2007
  - Results Database launched in September 2008
  - Currently 14,812 posted entries
- Design
  - Based on statutory requirements
  - Informed by CONSORT and other relevant standards
  - Requires “minimum data set” specified in protocol
  - Uses a tabular format for data with minimal narrative
- European drug regulator (EMA) developed a results database based on our model
  - Launched in October 2013

Results: NCT00137969

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

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

Text Size

A Study to Evaluate the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus (EXPLORER)

This study has been completed.

ClinicalTrials.gov Identifier:
NCT00137969

ceived: August 26, 2005
dated: August 16, 2013
rified: August 2013
of Changes

Disclaimer | How to Read a Study Record

First Received: June 5, 2009

ervention Model: Parallel Assignment;
ect, Investigator); Primary Purpose: Treatment

mic

ARTHRITIS & RHEUMATISM
Vol. 62, No. 1, January 2010, pp 222–233
DOI 10.1002/art.27233

Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus

The Randomized, Double-Blind, Phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab Trial

Joan T. Merrill,[1] C. Michael Neuwelt,[2] Daniel J. Wallace,[3] Joseph C. Shanahan,[4] Kevin M. Latinis,[5] James C. Oates,[6] Tammy O. Utset,[7] Caroline Gordon,[8] David A. Isenberg,[9] Hsin-Ju Hsieh,[10] David Zhang,[10] and Paul G. Brunetta[10]

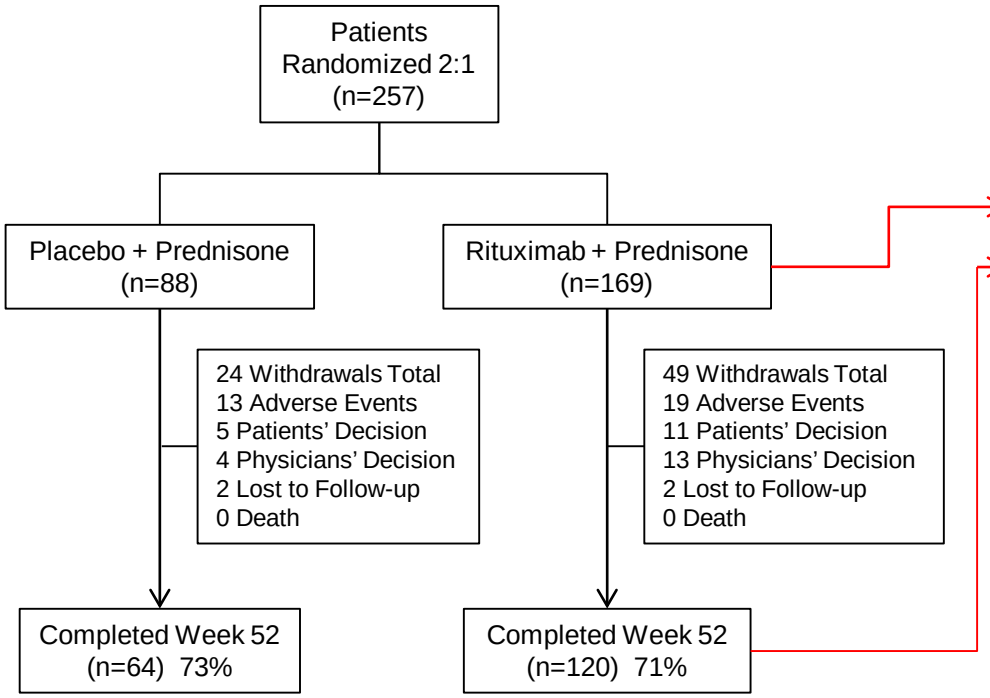
Objective. B cells are likely to contribute to the pathogenesis of systemic lupus erythematosus (SLE), and rituximab induces depletion of B cells. The Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial tested the efficacy and safety of rituximab versus placebo in patients with moderately-to-severely active extrarenal SLE.

Methods. Patients entered with ≥1 British Isles Lupus Assessment Group (BILAG) A score or ≥2 BILAG B scores despite background immunosuppressant therapy, which was continued during the trial. Prednisone was added and subsequently tapered. Patients were

ClinicalTrials.gov identifier: NCT00137969.
Supported by Genentech.
[1]Joan T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; [2]C. Michael Neuwelt, MD: Alameda County Medical Center, Oakland, California; [3]Daniel J. Wallace, MD: Cedars-

Results: Participant Flow

Publication (CONSORT Flow Diagram)



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Period 1: 52 Weeks

	Placebo + Prednisone	Rituximab + Prednisone
STARTED	**88**	**169**
COMPLETED	**64**	**120**
NOT COMPLETED	**24**	**49**
Adverse Event	13	19
Patients' Decision	5	11
Physicians' Decision	4	13
Lost to Follow-up	2	3
Death	0	3

Adapted from Merrill JT et al. *Arthrit Rheum* 2010 and NCT00137969

Results: Baseline Characteristics

Publication ("Table 1")

Table 1. Baseline demographic and disease characteristics of the patients*

Characteristic	Placebo (n = 88)	Rituximab (n = 169)
Female sex	93.2	89.9
Age, mean ± SD years	40.5 ± 12.8	40.2 ± 11.4
Race, %		
White	55.7	56.2
African American	27.3	23.7
Hispanic	9.1	14.2
Asian/Pacific Islander	5.7	3.6
Other	2.2	1.1
Disease duration, mean ± SD years	8.7 ± 7.6	8.5 ± 7.2
Long-term prednisone therapy†	53.4	58.6
Assigned prednisone dosage at screening, mg/kg/day		
0.5	61.4	62.7
0.75	29.5	32.0
1.0	9.1	5.3
Background immunosuppressive drug		
Azathioprine	36.4	32.0
Methotrexate	27.3	27.8
Mycophenolate mofetil	36.4	39.6

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Baseline Measures

	Placebo + Prednisone	Rituximab + Prednisone	Total
Number of Participants	88	169	257
Age [units: years] Mean ± Standard Deviation	40.5 ± 12.8	40.2 ± 11.4	40.3 ± 11.9
Gender [units: participants]			
Female	82	152	234
Male	6	17	23
Race [units: participants]			
White	49	95	144
African American	24	40	64
Hispanic	8	24	32
Asian/Pacific Islander	5	6	11
Other	2	2	4
Disease duration [units: years] Mean ± Standard Deviation	8.7 ± 7.6	8.5 ± 7.2	8.6 ± 7.3

Adapted from Merrill JT et al. *Arthrit Rheum* 2010 and NCT00137969

Results: Outcome Measures

Publication

"At week 52, no difference was noted in major clinical responses or partial clinical responses between the placebo group (15.9% had a major clinical response …) and the rituximab group (12.4% had a major clinical response …)"

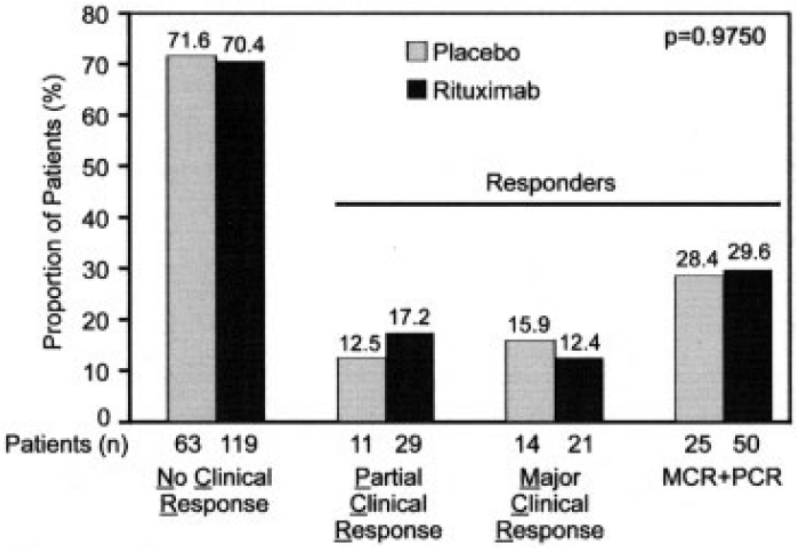

Figure 2A. Proportion of patients experiencing a major clinical response (MCR) … at 52 weeks

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Primary Outcome

Measure Title	**Participants Achieving Either a Major Clinical Response (MCR) or Partial Clinical Response (PCR) Defined by British Isles Lupus Assessment Group (BILAG) Scores Over the 52-week Treatment Period**
Measure Description	The BILAG Index is used for measuring clinical disease activity in Systemic Lupus …
Time Frame	Baseline to 52 weeks

Measured Values

	Placebo + Prednisone	**Rituximab + Prednisone**
Number of Participants Analyzed	88	169
[*units: participants*]		
MCR (excluding PCR)	14	21
PCR	11	29
Nonclinical Response	63	119

Adapted from Merrill JT et al. *Arthrit Rheum* 2010 and NCT00137969

Results: Adverse Events

Publication

Table 2. Adverse events in the safety population*

Adverse event	Placebo (n = 88)	Rituximab (n = 169)
Any treatment-emergent SAE	32 (36.4)	64 (37.9)
Any treatment-emergent SAE reported in ≥5% of patients		
Cardiac disorder	5 (5.7)	5 (3.0)
Infections and infestations	15 (17.0)	16 (9.5)
Gastrointestinal disorders	7 (8.0)	8 (4.7)
General disorder	5 (5.7)	7 (4.1)
Musculoskeletal and connective tissue disorders	5 (5.7)	9 (5.3)
Neutropenia	0 (0)	6 (3.6)
Any study drug–related treatment-emergent SAE	8 (9.1)	13 (7.7)
Any infusion-related AE	34 (38.6)	74 (43.8)
First infusion	26 (29.5)	46 (27.2)
Second infusion	14 (16.5)	29 (17.6)
Third infusion	7 (10.0)	23 (16.3)
Fourth infusion	4 (5.9)	25 (18.5)
Any infusion-related SAE	15 (17.0)	16 (9.5)
Any treatment-emergent infection-related SAE	15 (17.0)	16 (9.5)
Any treatment-emergent infection-related SAE reported in ≥2% of patients		
Lower respiratory tract and lungs	4 (4.5)	5 (3.0)
Bacterial	4 (4.5)	4 (2.4)
Abdominal and gastrointestinal	4 (4.5)	2 (1.2)
Sepsis, bacteremia, viremia, and fungemia NEC	3 (3.4)	2 (1.2)
Death	1 (1.1)	4 (2.4)

* Values are the number (%). SAE = serious adverse event; NEC = not elsewhere classified.

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Serious Adverse Events

	Placebo + Prednisone	Rituximab + Prednisone
Total # participants affected/at risk	**32/88 (36.36%)**	**68/169 (40.24%)**
Blood and lymphatic disorders		
Neutropenia	0/88 (0.00%)	6/169 (3.55%)
Pancytopenia	1/88 (1.14%)	1/169 (0.59%)
Haemolytic Anaemia	0/88 (0.00%)	1/169 (0.59%)
Lymphophenia	0/88 (0.00%)	1/169 (0.59%)
Thrombocytopenia	0/88 (0.00%)	1/169 (0.59%)
Cardiac disorders		
Coronary artery disease ….	…	…

Adapted from Merrill JT et al. *Arthrit Rheum* 2010 and NCT00137969

Key Concepts

- The Basic Results Database requires the reporting of what was done; it does not require a change in study design or study procedures;
- Quality Assurance is designed to ensure that results are complete and meaningful; it does not ensure that studies are valid, useful, or interesting!
- The intended audience is “readers of the medical literature.”

Data Submission Basics

- Web-based data entry system for summary protocol and results information
  - Requires organizational account, user name, password
- Structured data elements
  - Some required* and others optional
  - Pull-down menus and text
- Business rules/validation
  - ERROR - Study cannot be released; must be addressed
  - WARNING: - Should be addressed
  - NOTE - Helpful hints; may or may not apply

ClinicalTrials.gov

ClinicalTrials.gov Protocol Data Elen

January 2013

* Required by ClinicalTrials.gov
FDAAA Required to comply with US Public La
(FDAAA) May be required to comply with US Pu

. Titles and Background Information

Organization's Unique Protocol ID * FDAAA
Definition: Unique identification assigned to the protocol by the sponsoring orga
number. Multiple studies conducted under the same grant must each have a uniqu
(Limit: 30 characters)
Examples:
ABT-1233-RV
Merck-023
ACTG 021

Secondary IDs FDAAA
Definition: Other identification numbers assigned to the protocol, including uniq
applicable. (Limit: 30 characters)

ID Type Select one. Provide additional information, depending upon selec
- US NIH Grant/Contract Award Number - in the Secondary ID field,
components of the full award number (type code, support year and s
Examples: R01DA013131, UO1HL066582, 5R01HL123451-01A
- Other Grant/Funding Number - also provide name of grantor.
- Registry Identifier - also provide name of clinical trials registry.
- EudraCT Number - from European Union Drug Regulatory Authorit
- Other Identifier - also provide brief description (i.e., what organizati

Brief Title * FDAAA
Definition: Protocol title intended for the lay public. (Limit: 300 characters)
Example: Safety Study of Recombinant Vaccinia Virus Vaccine to Treat Prostate

Acronym
Definition: Acronym or initials used to identify this study, if applicable. Enter on
in parentheses following the brief title. (Limit: 14 characters)
Example:
Brief Title: Women's Health Initiative
Acronym: WHI
Displayed on ClinicalTrials.gov as: Women's Health Initiative (WHI)

Official Title
Definition: Official name of the protocol provided by the study principal investig
Example: Phase 1 Study of Recombinant Vaccinia Virus That Expresses Prostate
(Limit: 600 characters)

Study Type * FDAAA
Definition: Nature of the investigation. Select one.

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

November 2013

The "basic results" data element definitions and requirements currently included in ClinicalTrials.gov represent the National Institutes of Health's (NIH's) current thinking on this topic, and were developed in response to the provision contained within FDAAA that required the Agency to develop a "basic results" databank within one year of enactment. They do not create or confer any rights for or on any person and do not operate to bind NIH, the Department of Health and Human Services or the public. NIH will interpret these "basic results" reporting requirements in regulations or guidance to be issued at a later date. Prior to the issuance of draft regulations or guidance for comment, comments on the existing ClinicalTrials.gov "basic results" data element definitions and requirements are welcome and will be considered by the Agency in drafting a Notice of Proposed Rulemaking. Comments should be addressed to register@clinicaltrials.gov. Please include "Comments on ClinicalTrials.gov Results Requirements" in the subject line.

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

1. Results Point of Contact * : Point of contact for scientific information about the posted clinical trial results.

Name or Official Title * : For the designated individual. Note that this may be a specific person's name (e.g., Dr. Jane Smith) or a position title (e.g., Director of Clinical Trials)

Organization Name * : Full name of the designated individual's organizational affiliation.

Phone * : (or "Email" required) Office phone of the designated individual. Use the format 123-456-7890 within the United States and Canada. Otherwise, provide the country code and phone number.

Ext. : Phone extension, if needed

Email * : (or "Phone" required) Electronic mail address of the designated individual.

2. Certain Agreements * : Information certifying whether there exists an agreement between the sponsor or its agent and the principal investigators (unless the sponsor is an employer of the principal investigators) that restricts in any manner the ability of the principal investigators (PIs), after the completion 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. This does not include an agreement solely to comply with applicable provisions of law protecting the privacy of participants.

Are all PIs Employees of Sponsor? (Y/N) *: If all principal investigators are employees of the sponsor, select "Yes" and skip the remaining questions. If any principal investigator (PI) is not an employee of the sponsor, select "No" and answer the remaining questions.

Results Disclosure Restriction on PI(s)? (Y/N) [*] If there is an agreement between the sponsor (or its agent) and any non-employee PI(s) that restricts the PI's rights to discuss or publish trial results after the trial is completed, select "Yes" and select a "Restriction Type." Trial completion is defined as the final date on which data were collected. (ie, the Study Completion Date from the Protocol Data Elements)

If there are agreements with multiple non-employee PIs and there is a disclosure restriction on at least one PI, select "Yes" and answer the remaining question. If there are varying agreements with PIs, choose the type below that represents the most restrictive of the agreements (e.g., the agreement with the greatest embargo time period).

PI Disclosure Restriction Type : Select one

- 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** from the time submitted to the sponsor for review. 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

General Review Criteria

- Protocol and results must be clear and informative
- Review focuses on:
  - Logic and internal consistency
  - Apparent validity
  - Meaningful entries
  - Formatting, including appropriate use of database structure
- Not equivalent to peer review; not verified against external sources

Review Criteria: http://clinicaltrials.gov/ct2/manage-recs/resources

Examples of Incoherent Entries

- 823.32 mean hours sleep/day
- “time to survival”
- 36 eyeballs in study of 14 people
- “mean time to seizure” = 18 people
- “first occurrence of all cause mortality (adjudicated)”

ClinicalTrials.gov

ClinicalTrials.gov Status Update

And What We Have Found

ClinicalTrials.gov Reporting Volume
(as of 26 Oct 2015)

- Registration
  - 201,000+ study records
  - 500 submissions/week
  - > 14,100 data providers (sponsors and investigators)
- Summary Results Reporting
  - 18,700+ records with results posted
  - 100 submissions/week
  - > 2,200 data providers
- Usage Stats
  - 179+ million page views/month
  - 61,000+ unique visitors/day


WE ADDED A NEW PERFORMANCE TEST, BUT LEARNED THAT THE TEST ITSELF IS FLAWED.
Dilbert.com DilbertCartoonist@gmail.com
NOW OUR PRODUCT FAILS OUR OWN TESTS AND OUR CUSTOMERS ARE ASKING TO SEE THE TEST RESULTS.
8-11-10 ©2010 Scott Adams, Inc./Dist. by UFS, Inc
DO I HAVE PERMISSION TO FAKE THE TEST DATA?
I DIDN'T EVEN KNOW DATA CAN BE REAL.

Issues revealed by the results reporting requirements

- Lack of key competencies
- Complexity of studies
- Diffusion of responsibility

ClinicalTrials.gov

Lack of Key Competencies

- Certain types of errors reflect lack of understanding of trial design and analysis
- Sometimes this is related to the fact that the investigator is not involved in the data reporting
- Sometimes it is not…

Examples of Errors

- “Time to survival” listed as an outcome measure, without understanding that it is an illogical entry;
- More participants analyzed for an outcome measure than started the study (and no recognition that this was a problem);
- P-value reported, but investigator denied that it was based on a “statistical test”;
- Confidence interval reported, but no parameter listed (and investigator denied that there was a parameter)

“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)

Measures of Complexity

- Study Structure
  - Multiple Periods: Up to 10 per trial
  - Number of Arms: Up to 16 per trial
  - Factorial Design: Over 1,500 trials
- Number of Outcome Measures per Trial
  - Primary (POM): Up to 71
  - Secondary (SOM): Up to 122
  - All Reported OMs: Up to 124

Measures of Complexity
(continued)

- Number of Categories within an Outcome Measure
  - Up to 468
- Analysis Populations Used in a Single Trial
  - Up to 25 different “denominators” used for a single arm

Diffusion of Responsibility

- In order to enter results data, one must be able to:
  - Describe the participant flow
  - Describe the prespecified outcome measures (e.g., including units of measurement)
  - Identify the analysis population for each measure
- For many trials, nobody can be identified who can do this!
- Many investigators do not consider it their role
- When there is a journal article, not considered the author's role
- The statisticians cannot always explain what was done
- Who's role is it?

COMMENTARY

A Historical Perspective on Clinical Trials Innovation and Leadership

Where Have the Academics Gone?

David L. DeMets, PhD
Robert M. Califf, MD

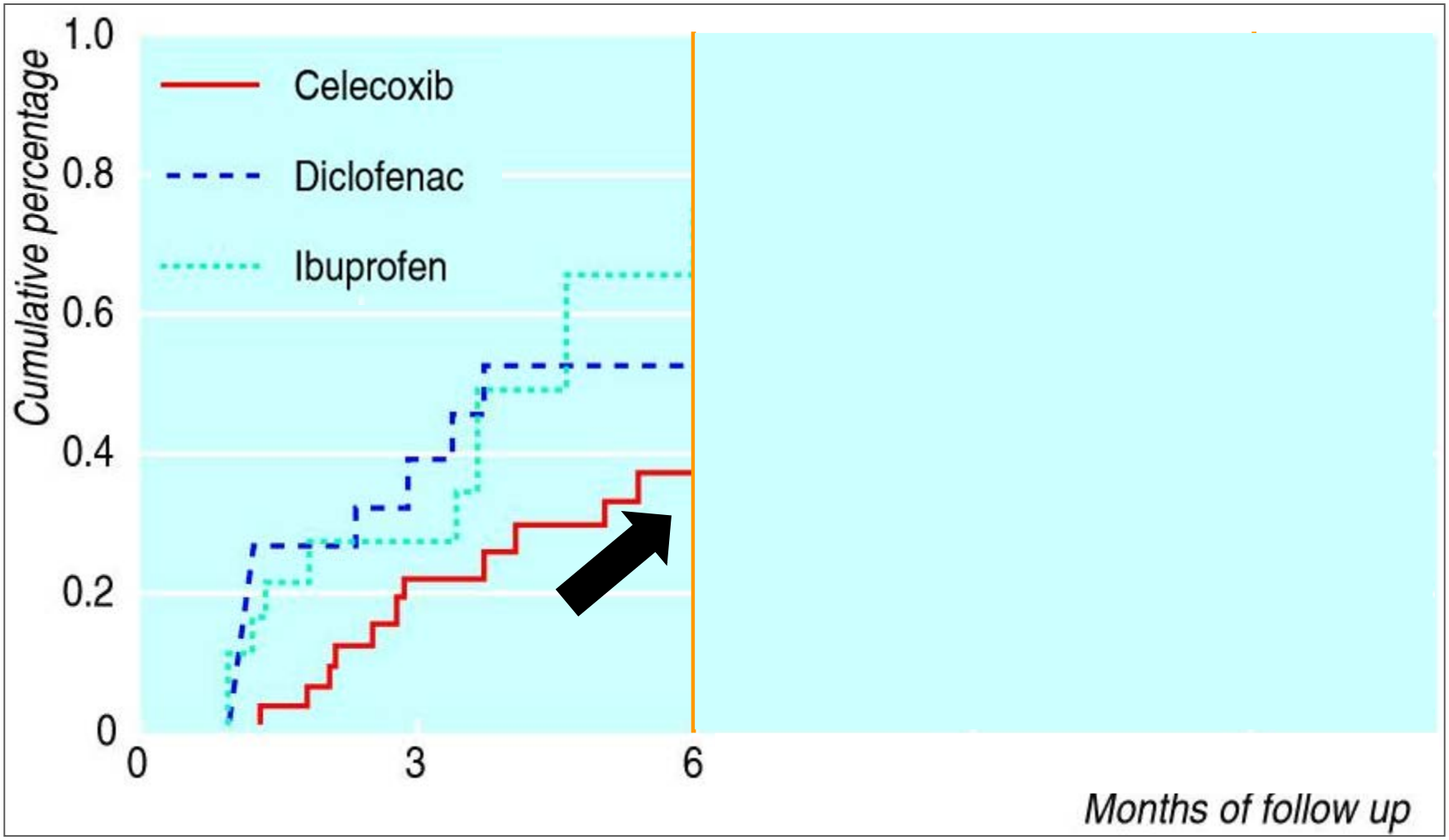
THE RANDOMIZED CONTROLLED TRIAL (RCT), THE GOLD standard for evaluating the balance of risk and benefit in medical therapies, first emerged as a key clinical research tool in the mid-20th century thanks to visionary leadership of agencies such as the US National Institutes of Health (NIH), the UK Medical Research Council, and academic research institutions. Since then, clinical trials activity has shifted from the NIH and academia into the purviews of the medical products industry and regulatory authorities. Recent emphasis on evidence-based medicine, patient-centered outcomes research,[1] and learning[2] and accountable[3] health care systems underscores the fact that most clinical trials fail to provide the evidence needed to inform medical decision making. However, the serious im-

When fundamental trials methodologies were being developed at the NIH in the 1960s, an NIH-commissioned task force delineated recommendations for organizing and conducting RCTs.[4] One significant early example is the Coronary Drug Project,[5] a joint effort among NIH sponsors, an academic coordinating center, and a steering committee of academic leaders. In the 1970s and 1980s, the NIH often convened academic leaders to identify knowledge gaps and prioritize and conduct specific trials as funding permitted.

During the 1960s, there was scant statistical literature examining clinical trials methodologies. Researchers learned by doing trials, noting successes and failures, and iterating to advance the field. In a series of discussions in the 1970s, ideas were debated and solutions to immediate problems were proposed.[6] Throughout the 1970s and 1980s, NIH and academic biostatisticians developed many methods now in routine use, including sample size estimation, interim data monitoring, and repeated measure methods for analysis.

Adherence to Study Protocol

Does Anybody Really Care?



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.

Source: Jüni P, Rutjes AW, Dieppe PA. *BMJ*. 2002 Jun 1;324(7349):1287-8.

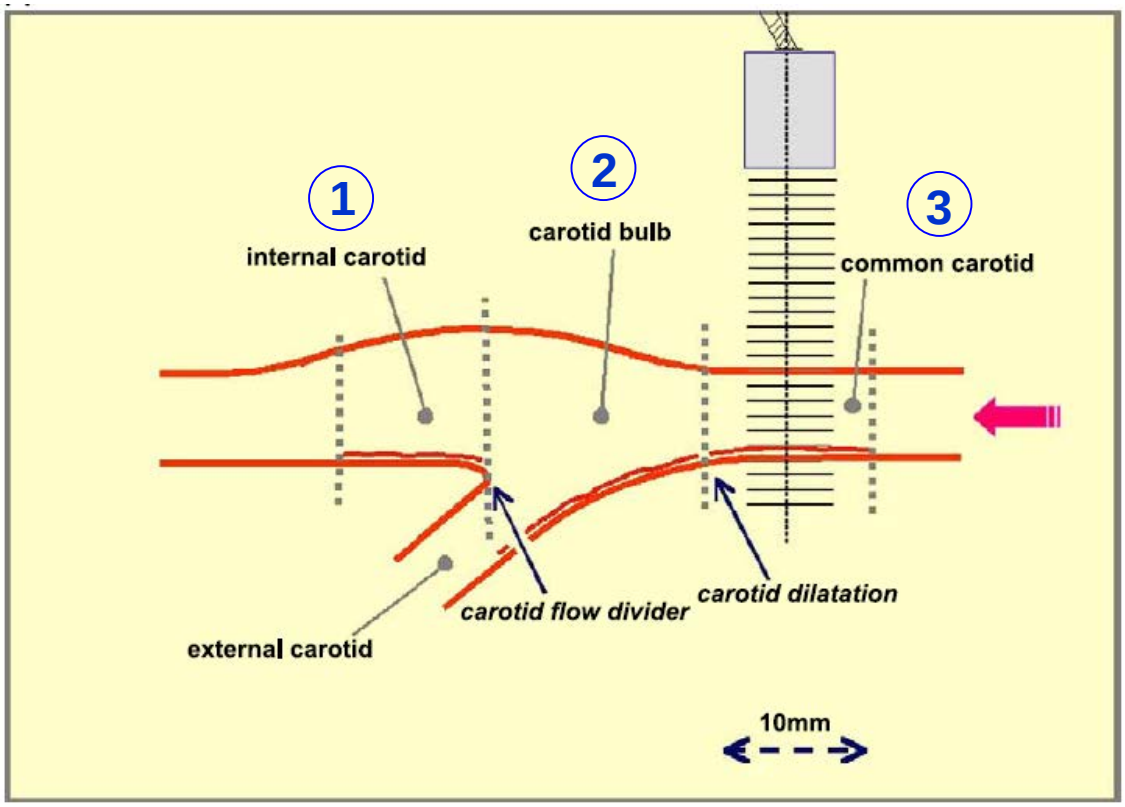
Internal Corporate Email

"They swallowed our story, hook, line and sinker…"

http://s3.documentcloud.org/documents/372382/celebrex2.pdf

ClinicalTrials.gov

ENHANCE (NCT00552097): Prespecified Endpoints



Source: Kastelein JJ et al. *Am Heart J*. 2005 Feb;149(2):234-9.

ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

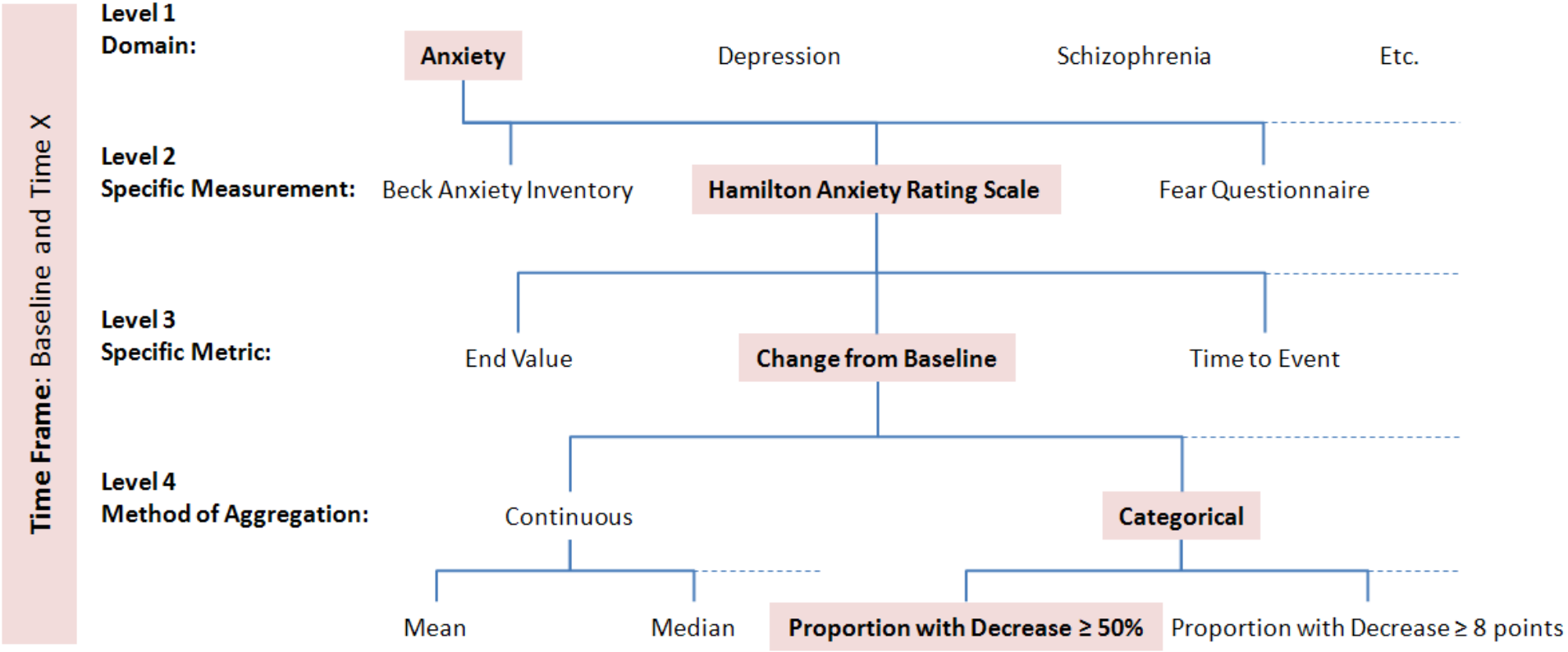
December 11, 2007

Mr. Fred Hassan
Chairman of the Board, Chief Executive Officer
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Mr. Richard T. Clark
Chairman of the Board, President, Chief Executive Officer
Merck & Co., Inc.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889

"…it appears that the study itself was not registered with ClinicalTrials.gov until October 31, 2007, a full 18 months after completion of the study. In addition, the endpoint indicated in the ClinicalTrials.gov web site[1] appears to differ from the endpoint described in the initial study design.[2]"

Specification in Reporting OMs



Source: Zarin et al. N *Engl J Med* 2011;364:852-60

NCT00136318 - Initial and Updated Entries for Primary Outcome Measures

Level of Specification	ClinicalTrials.gov Initial Entry	Publication
Domain (e.g., "anxiety")	Depression	Depression
Specific measurement (e.g., "Hamilton Anxiety Rating Scale")	HAM-D (Hamilton Depression Rating Scale)	MADRS (Montgomery–Asberg Depression Rating Scale)
Specific metric (e.g., "change from baseline")	N/A	MADRS score ≥13 during time frame
Method of aggregation (e.g., "proportion of participants with decrease 50%")	N/A	Percentage of participants with specific metric
Time frame (e.g., "12 weeks")	24 weeks	• 50 weeks after receiving intervention for participants with HCV genotype 1 or 4 OR • 26 weeks after receiving intervention for patients with HCV genotype 2 or 3

Zarin, Tse. *Ann Intern Med*. 2013 Jul 2;159(1):65-7.

Example of POM changes

- **Published Article**: "maximum percentage reversal of the anticoagulant effect"
  - Continuous measure
- **Final Protocol/SAP**: "The proportion of patients achieving at least 100%, 80% and 50% maximum reversal…"
  - Categorical measure
- **Registration** (at publication): "Maximum reversal of anticoagulant effect…"
  - *No* Method of Aggregation specified

Research

JAMA Internal Medicine
Formerly *Archives of Internal Medicine*

Original Investigation

Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial
A Randomized Clinical Trial

MAIN OUTCOMES AND MEASURES Breast cancer incidence was a prespecified secondary outcome of the trial for women without a prior history of breast cancer (n = 4152).

ISRCTN registry

ISRCTN35739639 DOI 10.1186/ISRCTN35739639

Effects of Mediterranean diet on the primary prevention of cardiovascular disease

Primary outcome measures

A composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Secondary outcome measures

Death of any cause and incidence of angina leading to a revascularisation procedure, heart failure, diabetes mellitus, dementia, and cancer.

Other outcomes:
1. Changes in blood pressure
2. Body weight
3. Adiposity measures
4. Blood sugar
5. Lipid profile
6. Markers of inflammation
7. Other intermediate markers of cardiovascular risk

Toledo E et al. *JAMA Intern Med*. 2015 Sep 14:1-9. [Epub ahead of print]

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Sample Issues

Reproducible Research on Discrepant Reporting of Results

	Hartung et al. (2014)	Becker et al. (2014)
Sample	Phase 3 & 4 trials with results on Clinicaltrials.gov & journal publication	Trials with results on ClinicalTrials.gov & high-impact journal publication
Key Discrepancies		
POM Descriptions	15%	15%
POM Values	20%	16%
SAEs	35% (Frequent underreporting or omissions in publication)	39% (Frequent underreporting or omissions in publication)
Other AEs	37% (Among ≥1 AE reported on ClinicalTrials.gov)	48% (Among all trials)

Hartung et al. *Ann Intern Med*. 2014:477-83; Becker et al. *JAMA*. 2014: 1063-5.

Reporting of Noninferiority Trials: ClinicalTrials.gov and Publications

- Sample: 344 records on ClinicalTrials.gov from 338 articles, described as noninferiority (NI) trials

	ClinicalTrials.gov	Publication
Description of NI design	99 (28.8%)	344 (100%)
Provided NI margins	15 (4.4%)*	340 (98.8%)
Justification for NI margins	N/A	95 (27.6%)
NI analyses and results	76/129 (22.1%) of results posted	342 (99.4%)

*all 15 concordant

Gopal AD et al. *JAMA*. 2015 Mar 17;313(11):1163-5.

ClinicalTrials.gov

NCT00058825: Percentage of Participants with 95% Confidence Interval

3. Primary Outcome

Title:	Percentage of Participants Achieving an Hemagglutination Inhibition (HI) Antibody Titer of 1:40 or More 21 Days After First Study Vaccination
▼Description:	[No text entered]
Time Frame:	21 days after the first study vaccination
Safety Issue?	No

▼Outcome Measure Data ✓

▶Analysis Population Description

Arm/Group Title	**Placebo Cohort A**	**CSL425 (7.5 Mcg) Cohort A**	**CSL425 (15 Mcg) Cohort A**	**Placebo Cohort B**	**CSL425 (7.5 Mcg) Cohort B**	**CSL425 (15 Mcg) Cohort B**
▼Arm/Group Description:	Placebo, Aged 6 months to less than 3 years	7.5 mcg of hemagglutinin antigen per dose, Aged 6 months to less than 3 years	15 mcg of hemagglutinin antigen per dose, Aged 6 months to less than 3 years	Placebo, Aged 3 years to less than 9 years	7.5 mcg of hemagglutinin antigen per dose, Aged 3 years to less than 9 years	15 mcg of hemagglutinin antigen per dose, Aged 3 years to less than 9 years
Number of Participants Analyzed	25	102	89	27	104	102
Number (95% Confidence Interval) Units: percentage of participants	**8.0 (1.0 to 26.0)**	**90.2 (82.7 to 95.2)**	**84.3 (75.0 to 91.1)**	**25.9 (11.1 to 46.3)**	**84.6 (76.2 to 90.9)**	**89.2 (81.5 to 94.5)**

NCT01903005: Number of Participants with 95% Confidence Interval

5. Secondary Outcome

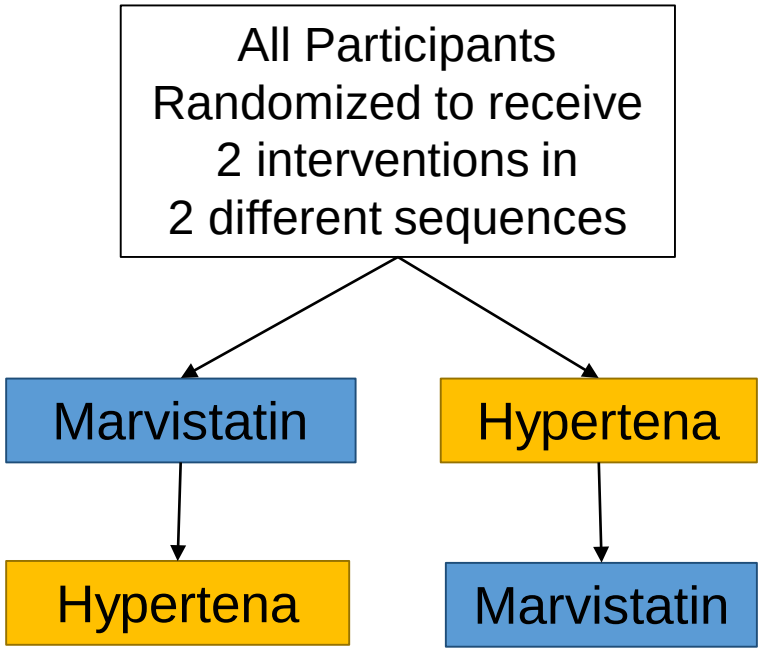
Title:	Retention in Treatment in the Safety Population
▼Description:	Retention in treatment by visit in the safety population at weeks 4, 8, 12, 16, 20, and 24, defined as the number of patients receiving treatment on the day of the visit (± 5 days for each visit)
Time Frame:	Treatment retention was assessed at weeks 4, 8, 12, 16, 20, and 24
Safety Issue?	No

▼Outcome Measure Data ✓

▸Analysis Population Description

Arm/Group Title	Safety Population
▼Arm/Group Description:	Weeks 1-24: Higher bioavailability BNX sublingual tablets (open-label) were titrated at doses ranging from 5.7/1.4 mg to 17.1/4.2 mg, to a dose that relieved opioid cravings and withdrawal symptoms with minimal side effects.
Number of Participants Analyzed	665
Number (95% Confidence Interval) Units: participants	
Week 4	563 (545 to 581)
Week 8	483 (460 to 505)
Week 12	425 (401 to 450)
Week 16	383 (358 to 408)
Week 20	333 (308 to 358)

Example 2-way Crossover Design



ClinicalTrials.gov

Example 2-way Crossover Participant Flow

Period 1: 1st Intervention

	Marvistatin then Hypertena	Hypertena then Marvistatin
Started	111	111
Completed	108	111
Not Completed	**3**	**0**
Adverse Event	1	0
Protocol Violation	2	0

Period 2: 2nd Intervention

	Marvistatin then Hypertena	Hypertena then Marvistatin
Started	108	111
Completed	105	110
Not Completed	**3**	**1**
Adverse Event	2	0
Protocol Violation	1	1

ClinicalTrials.gov

Acceptable Baseline Arms for Crossover?

FDAAA says that Baseline Data must be reported for each arm and the overall study population.

Is this acceptable? If not, how should Arms be separated?

Baseline Characteristics

Reporting Groups

	Description
All participants	All enrolled and randomized participants

Baseline Measures

	Total
Overall Number of Baseline Participants	**28**
Age Categorical Measure Type: Number Units: participants	
<=18 years	**0**
Between 18 and 65 years	**28**
>= 65 years	**0**
Age Continuous Mean (Standard Deviation) Units: years	**32.6 (5.7)**

Interim Results or DSMB-Halted Trials

- Displaying interim results collected for a trial?
- Role of ClinicalTrials.gov Results Database for DSMB-Halted Trials? e.g.,
  - **NCT01206062**: NHLBI's Systolic Blood Pressure Intervention Trial (SPRINT)
  - **NIH Press Release (9/11/15)**: "NIH stopped the blood pressure intervention earlier than originally planned in order to quickly disseminate the significant preliminary results."
  - ***New York Times* Op-Ed (Topol & Krumholz, 9/17)**: "The problem is that many details of the study have not been released. It will be months before the study is presented at a major scientific meeting and possibly even longer before it is published."

Embargoed for Release: Friday, September 11, 2015, 10:30 a.m. EDT

Landmark NIH study shows intensive blood pressure management may save lives

Lower blood pressure target greatly reduces cardiovascular complications and deaths in older adults

Institute/Center

National Heart, Lung, and Blood Institute (NHLBI)

Contact

NHLBI Engagement and Media Relations Branch
301-496-4236

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More intensive management of high blood pressure, below a commonly recommended blood pressure target, significantly reduces rates of cardiovascular disease, and lowers risk of death in a group of adults 50 years and older with high blood pressure. This is according to the initial results of a landmark clinical trial sponsored by the National Institutes of Health called the Systolic Blood Pressure Intervention Trial (SPRINT). The intervention in this trial, which carefully adjusts the amount or type of blood pressure medication to achieve a target systolic pressure of 120 millimeters of mercury (mm Hg), reduced rates of cardiovascular events, such as heart attack and heart failure, as well as stroke, by almost a third and the risk of death by almost a quarter, as compared to the target systolic pressure of 140 mm Hg.

"This study provides potentially lifesaving information that will be useful to health care providers as they consider the best treatment options for some of their patients, particularly those over the age of 50," said Gary H. Gibbons, M.D., director of the National Heart, Lung, and Blood Institute (NHLBI), the primary sponsor of SPRINT. "We are delighted to have achieved this important milestone in the study in advance of the expected closure date for the SPRINT trial and look forward to quickly communicating the results to help inform patient care and the future development of evidence-based clinical guidelines."

"Our results provide important evidence that treating blood pressure to a lower goal in older or high-risk patients can be beneficial and yield better health results overall."

—**Lawrence Fine, M.D.**
Chief, Clinical Applications and Prevention Branch at NHLBI

High blood pressure, or hypertension, is a leading risk factor for heart disease, stroke, kidney failure, and other health problems. An estimated 1 in 3 people in the United States has high blood pressure.

The SPRINT study evaluates the benefits of maintaining a new target for systolic blood pressure, the top number in a blood pressure reading, among a group of patients 50 years and older at increased risk for heart disease or who have kidney disease. A systolic pressure of 120 mm Hg, maintained by this more intensive blood pressure intervention, could ultimately help save lives among adults age 50 and older who have a combination of high blood pressure and at least one additional risk factor for heart disease, the investigators say.

The New York Times

Don't Delay News of Medical Breakthroughs

By ERIC J. TOPOL and HARLAN M. KRUMHOLZ SEPT. 17, 2015

IN this age of instant information, medicine remains anchored in the practice of releasing new knowledge at a deliberate pace. It's time for medical scientists to think differently about how quickly they alert the public to breakthrough findings.

Last week the National Institutes of Health announced that it had prematurely ended a large national study of how best to treat people with high blood pressure because of its exceptional results.

In this trial of more than 9,000 people age 50 and older with high blood pressure, an aggressive treatment strategy to keep systolic blood pressure below 120 was compared with a conventional one aimed at keeping it below 140. The subjects all had a high risk of heart attacks, stroke and heart failure. The N.I.H. concluded, six years into a planned eight-year study, that for these patients, pushing blood pressure down far below currently recommended levels was very beneficial.

Ending a study early is rather unusual. In such cases, studies are stopped not by the investigators, but by an independent group of expert scientists who monitor the trial for evidence of unexpected harm or benefit that requires swift action. When a trial is halted early it is a surprise to the researchers who must not only move quickly to notify the participating doctors and subjects, but also decide how to communicate the results. The usual practice is to make a public announcement with an interpretation of the findings and then finalize the database and write the paper.

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

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail Text Size

Systolic Blood Pressure Intervention Trial (SPRINT)

This study is ongoing, but not recruiting participants.

Sponsor:
Wake Forest Baptist Health

Collaborators:
National Heart, Lung, and Blood Institute (NHLBI)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute on Aging (NIA)

Information provided by (Responsible Party):
David Reboussin, Wake Forest University Baptist Medical Center

ClinicalTrials.gov Identifier:
NCT01206062

First received: September 20, 2010
Last updated: May 17, 2013
Last verified: May 2013
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

Elevated blood pressure (BP) is an important public health concern. It is highly prevalent, the prevalence may be increasing, and it is a risk factor for several adverse health outcomes, especially coronary heart disease, stroke, heart failure, chronic kidney disease, and decline in cognitive function. The Systolic Blood Pressure Intervention Trial (SPRINT) is a 2-arm, multicenter, randomized clinical trial designed to test whether a treatment program aimed at reducing systolic blood pressure (SBP) to a lower goal than currently recommended will reduce cardiovascular disease (CVD) risk.

Condition	Intervention
Hypertension	Other: Intensive control of SBP Other: Standard BP arm

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Single Blind (Outcomes Assessor)
Primary Purpose: Treatment

Official Title: Systolic Blood Pressure Intervention Trial

ClinicalTrials.gov

What's an Individual Clinical Trial?

Definition of a Single Clinical Trial

- One defined cohort of participants
- One core protocol
- Planned analysis that involves the data from the one protocol

Tse T et al. *Principles and Practice of Clinical Research. 3rd ed.* 2012: 171-81.

Challenging situations

- Observational follow-on studies to an RCT
- Comparisons of arms from different studies
- Follow-on study designs?
  - Considered a “single” trial when defined in protocol and include same participants as original study
  - Consider a “separate” trial if re-consent is required or includes new participants (not part of original study)

Newer Trial Designs

- Adaptive trials (e.g., I-SPY 2)
  - Multiple arms, each representing a different drug
  - Arms/drugs “graduate” or get dropped
  - When should results be reported?
- Basket studies (e.g., MATCH)
  - Diagnostic test(s) done to assign participants to specific studies
  - What is a single study?

Looking Ahead

ICMJE 21st Data Element: Data Sharing

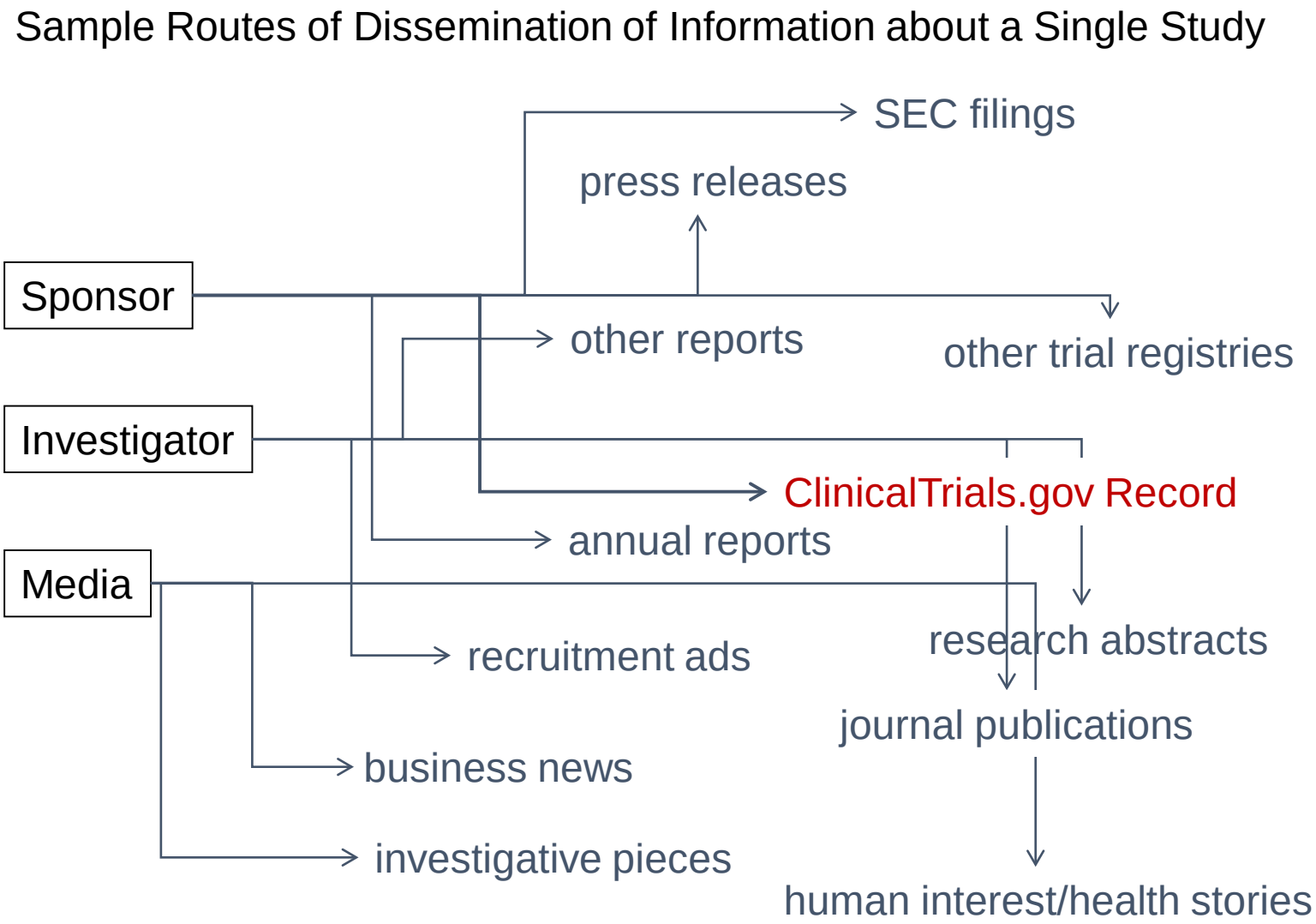
- Plan to Share Individual Participant-level Data (IPD)? (Yes/No/Undecided)
  - **Description**: If IPD collected in this study is to be made available, briefly describe what data are to be shared, availability time frame and how the data may be requested.
- Shared Study Documents
  - **Type**: e.g., Participant Level Data Set, Full Protocol, Informed Consent Form
  - **URL**: Web site where data or study document can be accessed, downloaded, or requested, if applicable.
  - **Comments**: Additional information such as instructions for requesting the data or document, as desired

Potential Role for ClinicalTrials.gov

- Provide framework and access to key trial information
  - Registration
  - Results
  - Links
  - Documents
- Provide context for available information
  - List of all trials for given topic
  - Documentation of what information is available for each trial
  - Help to avoid “disclosure biases” of all sorts

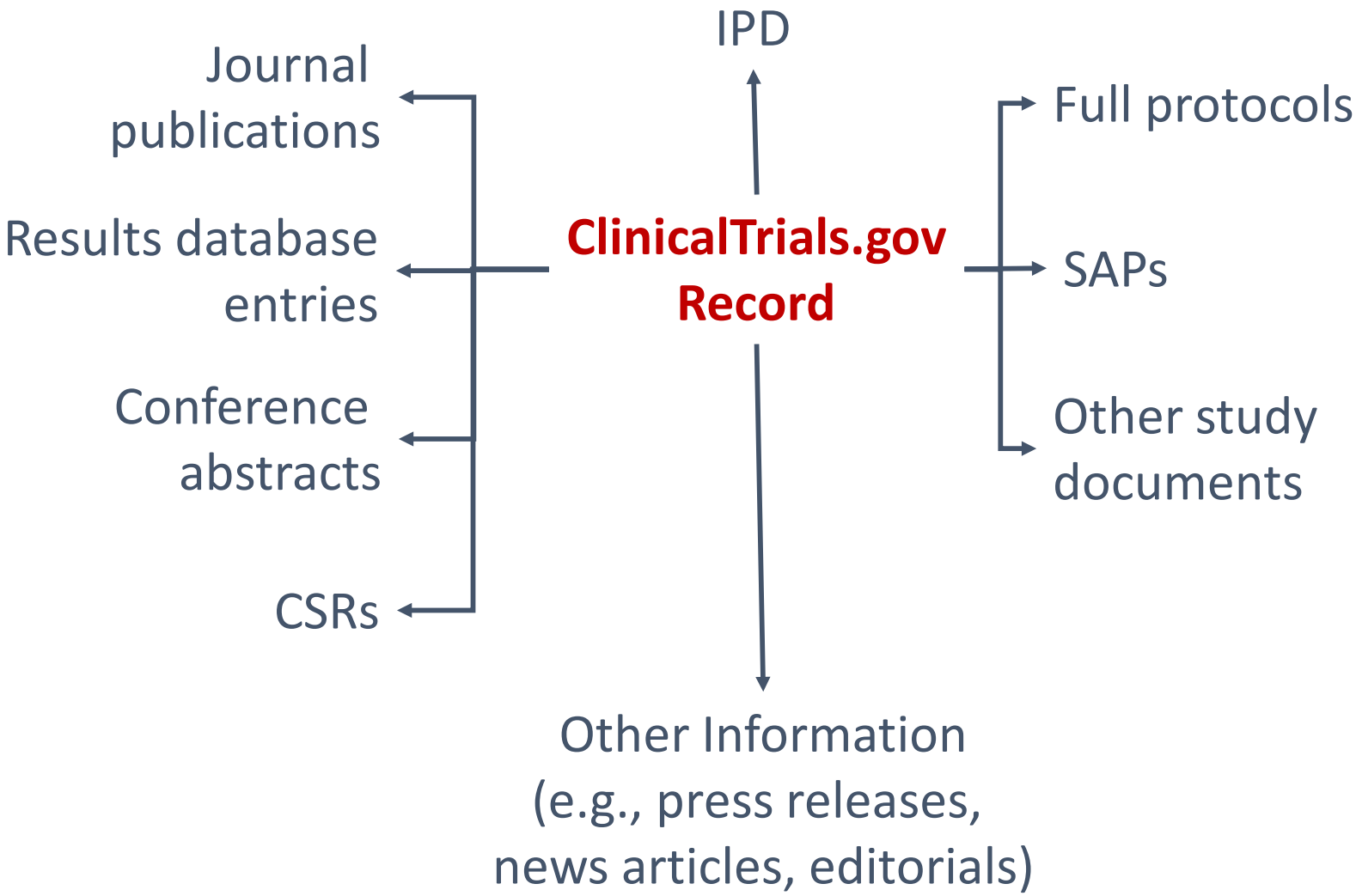
“Informational Chaos”

Diffuse, hard-to-access information about a single study



ClinicalTrials.gov

ClinicalTrials.gov: Informational Scaffold



ClinicalTrials.gov

Need for Organizational Infrastructure to Support Results Reporting

ClinicalTrials.gov Reporting: Strategies for Success at an Academic Health Center

Erin K. O'Reilly, Ph.D., R.A.C.[1,2], Nancy J. Hassell, C.C.R.P.[3], Denise C. Snyder, M.S., R.D.[2,4], Susan Natoli, M.S.W., C.C.R.P.[2,4], Irwin Liu, Ph.D.[2,5,6], Jackie Rimmler, M.S.[2,5], Valerie Amspacher, B.S.[1,2], Bruce K. Burnett, Ph.D., R.A.C.[1,2], Amanda B. Parrish, Ph.D. R.A.C.[1,2], Jelena P. Berglund, Ph.D., R.A.C.[1,2], and Mark Stacy, M.D.[2,7]

Abstract

The Food and Drug Administration Amendments Act of 2007 (FDAAA 2007, US Public Law 110-98) mandated registration and reporting of results for applicable clinical trials. Meeting these registration and results reporting requirements has proven to be a challenge for the academic research community. Duke Medicine has made compliance with registration and results reporting a high priority. In order to create uniformity across a large institution, a written policy was created describing requirements for clinical trials disclosure. Furthermore, a centralized resource group was formed with three full time staff members. The group not only ensures compliance with FDAAA 2007, it also acts as a resource for study teams providing hands-on support, reporting, training, and ongoing education. Intensive resourcing for results reporting has been crucial for success. Due to implementation of the institutional policy and creation of centralized resources, compliance with FDAAA 2007 has increased dramatically at Duke Medicine for both registration and results reporting. A consistent centralized approach has enabled success in the face of changing agency rules and new legislation. Clin Trans Sci 2015; Volume 8: 48–51.

Keywords: trials registration, trials reporting, FDAAA 2007, ClinicalTrials.gov, applicable clinical trial

Introduction

Examples of selective publication bias historically made the case for clinical trials registries,[1] and led to the posting of the Clinical Trials Data Bank (http://clinicaltrials.gov) in February 2000 in response to the Food and Drug Administration Modernization Act of 1997 (FDAMA). Section 113 of FDAMA required the establishment of a registry for clinical trials of experimental treatments (drug and biological) for patients with serious or life-threatening diseases or conditions. Since then, the registry has been widely expanded to accommodate the requirements of FDAAA 2007. Specifically, section 801 of the Food and Drug Administration Amendments (ICMJE) incorporated the requirement for registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.[4,5] While only 14 journals are official members of the ICMJE, over 1,600 other medical journals have purportedly committed to follow ICMJE recommendations.[6]

Finally, in addition to legal, funding, and publication considerations, mandatory inclusion of the NCT number on Medicare claims for routine costs of qualifying clinical trials became effective as of January 2014. Thus, studies that would not require

Clin Transl Sci. 2015 Feb;8(1):48-51.

ClinicalTrials.gov

Select Publications

Available at: http://www.clinicaltrials.gov/ct2/resources/pubs

Williams RJ, Tse T. DiPiazza K, Zarin DA. Terminated trials in the ClinicalTrials.gov results database: evaluation of availability of primary outcome data and reasons for termination. *PLoS One*. 2015 May 26;10(5):e0127242.

Zarin DA, Tse T, Ross JS. Trial-results reporting and academic medical centers. *N Engl J Med*. 2015 May 20. Epub.

Hartung DM, Zarin DA, Guise JM, et al. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Ann Intern Med*. 2014 Apr 1;160(7):477-83.

Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA*. 2012;307(17):1838-47.

Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross-sectional analysis. *BMJ*. 2012;344:d7292.

Other Relevant Policies

- **WHO** – Registration of all interventional studies
- **Declaration of Helsinki** – Registration of all human studies
- **EMA** – Registration and summary results reporting for all EU drug trials
- **CMS** – Registration of trials used for Coverage with Evidence Development (CED) and summary results reporting (or publication)
- **VA –** Registration and summary results reporting for all Office of Research and Development-funded clinical trials
- **PCORI –** Registration and summary results reporting for all PCORI-funded clinical studies