Update on Trial Reporting Requirements

Deborah A. Zarin, M.D.
Director, ClinicalTrials.gov
November 2016

Traditional System

- Design and conduct of clinical trials was left to individual investigators
  - No specific training required
  - Not much oversight of analytic methods
    - E.g., absence of scientific review of protocols at institutional level
- Individual investigators decided whether, when and how to disseminate results of clinical trials
  - Institutions assumed that fundamental academic incentives would ensure that this would happen;
  - But widespread appreciation that not all results would be reported

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Policies that Disrupted the Status Quo

Reporting Requirement	FDAAA NPRM (Proposed 2014)	Draft NIH Policy (Proposed 2014)	ICMJE Policy (Enacted 2005)
Scope	Registration & Results Reporting	Registration & Results Reporting	Registration
Phase	Not Phase 1	All	All
Intervention Type	Drugs, Biologics, & Devices regulated by the FDA	All	All
Funding	Any	NIH	Any
Enforcement	Up to $10,000/day; Loss of US Federal funding	Loss of NIH funding	Refusal to publish

New World Order

- We have examined the CRE and it's not pretty
  - Many poorly designed studies
  - Lack of fidelity to trial protocols (or lack of firm protocols)
  - Selective reporting
- FDAAA and NIH policies explicitly hold institutions accountable for reporting of their clinical trials
- **A lot of work to be done**

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The National Cancer Institute Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials

Notice Number: NOT-CA-15-011

Key Dates

Release Date: January 28, 2015

Related Announcements

none

Issued by

National Cancer Institute (NCI)

"When the final NIH Policy on Dissemination of NIH-Funded Clinical Trial Information is implemented, all NIH-funded investigators including NCI investigators will be subject to the NCI policy. The NCI Trial Access policy… will then be updated accordingly or withdrawn."

Purpose

The National Cancer Institute (NCI) announces its new policy aimed at ensuring public availability of results from NCI-supported clinical trials. This policy, referred to as the NCI Clinical Trial Access Policy, applies to all NCI funded research grant, cooperative agreements, and/or contracts that support covered interventional clinical trials.

This new policy reflects comments received in response to NCI's Request for Information announced in the NIH Guide for Grants and Contracts Notices released September 30, 2013 (NOT-CA-13-019) and November 4, 2013 (NOT-CA-14-005).

On November 19, 2014, the National Institutes of Health (NIH) issued a Request for Public Comments on the "Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information" (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html). When the final NIH Policy on Dissemination of NIH-Funded Clinical Trial Information is implemented, all NIH-funded investigators including NCI investigators will be subject to the NIH policy. The NCI Clinical Trial Access policy, announced by this Notice, will then be updated accordingly or withdrawn.

The NCI Clinical Trial Access Policy (full text)

I. Principles

Consistent with the mission of the National Cancer Institute ("NCI") to provide evidence-based approaches to cancer therapy, NCI believes that the full value of NCI-Supported Interventional Clinical Trials can be realized only if the final results of clinical trials are published as rapidly as possible. Timely and comprehensive access to the final results of clinical trials by investigators, clinicians and patients is particularly important for interventional cancer research studies because of their potential to directly impact patient care.

NEWS RELEASES

Friday, September 16, 2016

HHS takes steps to provide more information about clinical trials to the public

In an effort to make information about clinical trials widely available to the public, the U.S. Department of Health and Human Services today issued a final rule pdf that specifies requirements for registering certain clinical trials and submitting summary results information to ClinicalTrials.gov. The new rule expands the legal requirements for submitting registration and results information for clinical trials involving U.S. Food and Drug

Institute/Center

NIH Office of the Director (OD)

Contact

NIH News Media Branch
301-496-5787

Additional Information

- Federal Register Notice: HHS Final Rule pdf
- Federal Register Notice: NIH Policy pdf
- Summary of Changes: HHS Final Rule and NIH Policy
- Summary Table: HHS Final Rule and NIH Policy
- JAMA: Toward a New Era of Trust and Transparency in Clinical Trials
- NEJM: The Final Rule for US

FEDERAL REGISTER

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Part II

Department of Health and Human Services

42 CFR Part 11
Clinical Trials Registration and Results Information Submission; Final Rule

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

Notice Number: NOT-OD-16-149

Key Dates

Release Date: September 16, 2016
Effective Date: January 18, 2017

Related Announcements

NOT-OD-15-019

Issued by

National Institutes of Health (NIH)

Purpose

Summary

The National Institutes of Health (NIH) is issuing this policy to promote broad and responsible dissemination of information from NIH-funded clinical trials through ClinicalTrials.gov. The policy establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results information of these trials is submitted to ClinicalTrials.gov. The policy is complementary to the statutory and regulatory reporting requirements. These are section 402(j) of the Public Health Service Act, as amended by Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA), and the regulation Clinical Trial Registration and Results Information Submission, at 42 CFR Part 11. Hereafter, we refer to section 402(j) as the statute and 42 CFR Part 11 as the rule or regulation. This policy as well as the rule were posted in the Federal Register.

Supplemental Information

On November 19, 2014, and in tandem with the publication of the Notice of Proposed Rulemaking (NPRM) on Clinical Trial Registration and Results Submission, the NIH issued a complementary draft policy for public comment on the Dissemination of NIH-funded Clinical Trial Information[1,2]. The draft policy proposed that all NIH-funded awardees and

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Trial Reporting in ClinicalTrials.gov — The Final Rule

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., and Sarah Carr, B.A.

Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA) expanded the legal mandate for sponsors and others responsible for certain clinical trials of FDA-regulated drug, biologic, and device products to register their studies and report summary results information to ClinicalTrials.gov,[1] which is managed by the National Library of Medicine at the National Institutes of Health (NIH). The statute expanded registration requirements and provided a legally defined timeline with specific requirements for the systematic reporting of summary trial results. Although statutory components took effect before 2010, the FDAAA directed the Department of Health and Human Services (HHS) to issue regulations regarding certain statutory provisions and to consider possible expansion of the requirements through rulemaking.

developed the final rule, which was made publicly available on September 16, 2016. Simultaneously, the NIH issued a complementary final policy, under which NIH-funded awardees and investigators will be expected to submit registration and results information for all NIH-funded clinical trials, whether or not the trials are covered by the FDAAA requirements.[6]

Here, we summarize and highlight key points about the final rule (see box).

BACKGROUND

The FDAAA established legal requirements for sponsors and designated principal investigators (i.e., responsible parties) to report specified clinical trial information for certain applicable clinical trials to ClinicalTrials.gov. In addition to registration, the statute established a system and man-

Source: DOI:10.1056/NEJMsr1611785

Key Clinical Trial Reporting Requirements

Reporting Requirement	ICMJE Policy (Effective in 2005)	FDAAA Final Rule (Issued in 2016)	Final NIH Policy (Issued in 2016)
Scope	Registration	Registration & Results Reporting	Registration & Results Reporting
Phase	All	Not Phase 1	All
Intervention Type	All	Drugs, Biologics, & Devices regulated by the FDA	All (e.g., including behavioral interventions)
Funding Source	Any	Any	NIH
Enforcement	Refusal to publish	Criminal proceedings and civil penalties (up to $10,000/day); Loss of HHS funding	Loss of NIH funding

Effective Date Jan 18, 2017

- FDAAA Final Rule Requirements
  - Registration: Study Start Date ≥ January 18, 2017
  - Summary Results: Primary Completion Date ≥ January 18, 2017

- NIH Policy Requirements
  - Study Start Date ≥ January 18, 2017

  AND
  - Funding application (e.g., grants, other transactions, contracts) first submitted ≥ January 18, 2017

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Scope of Reporting Policies

- FDAAA- Final Rule (42 CFR Part 11)
  - Non-phase 1 interventional studies (clinical trials) of drug, biologic or devices
  - Includes IND exempt studies
  - Includes single arm trials
  - Includes studies of diagnostic technologies, including in vitro diagnostics
  - Includes studies of unapproved products
- NIH trial reporting policies
  - All NIH funded interventional studies (clinical trials)
  - Includes phase 1; studies without drugs/devices; etc

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Other Changes under Final Rule

- Can “opt out” of device lockbox
- Additional baseline measures required
  - Race/ethnicity
  - Measures associated with outcome measures
- Full protocol/SAP must be submitted with results
- All cause mortality data must be submitted
- Records posted after 30 days regardless of QC status

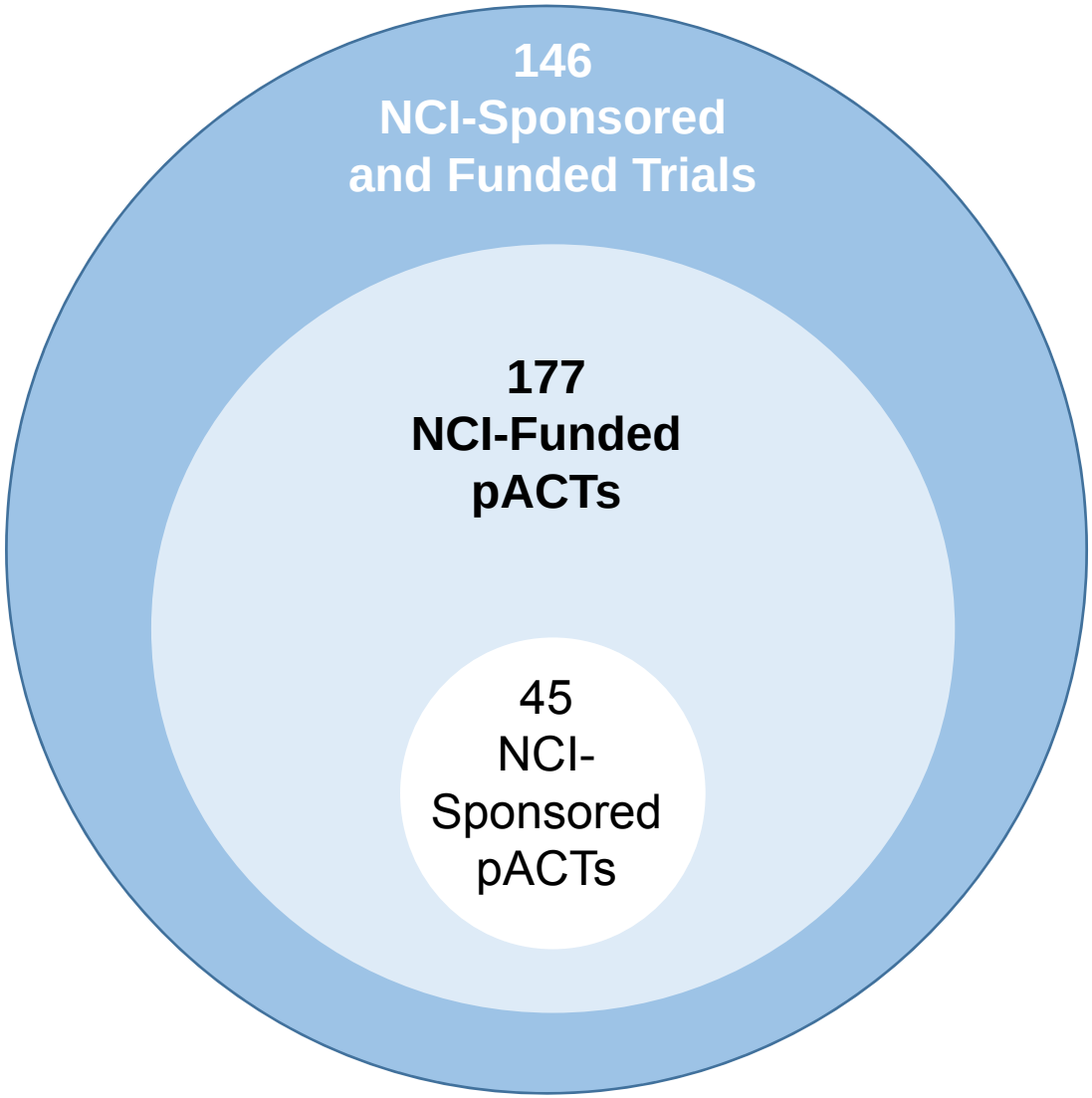
ClinicalTrials.gov

NIH IC Extramural Staff need to monitor Broader set of Trials

- FDAAA: ACTs
  - NIH plans to withhold funding to sponsors of NIH-funded ACTs that cannot be verified to be compliant
  - Following full implementation, external parties can generally determine compliance
- NIH Policy: All NIH-funded clinical trials
  - Applies to funding applications after Jan 18, 2017 for trials initiated after Jan 18, 2017
  - Must ensure registration and results reporting
  - Systems may need to be altered

ClinicalTrials.gov

NCI Trials that Started in 2015



368 Total NCI-Sponsored and Funded Interventional Studies (pACTs + Trials)

The Results Database

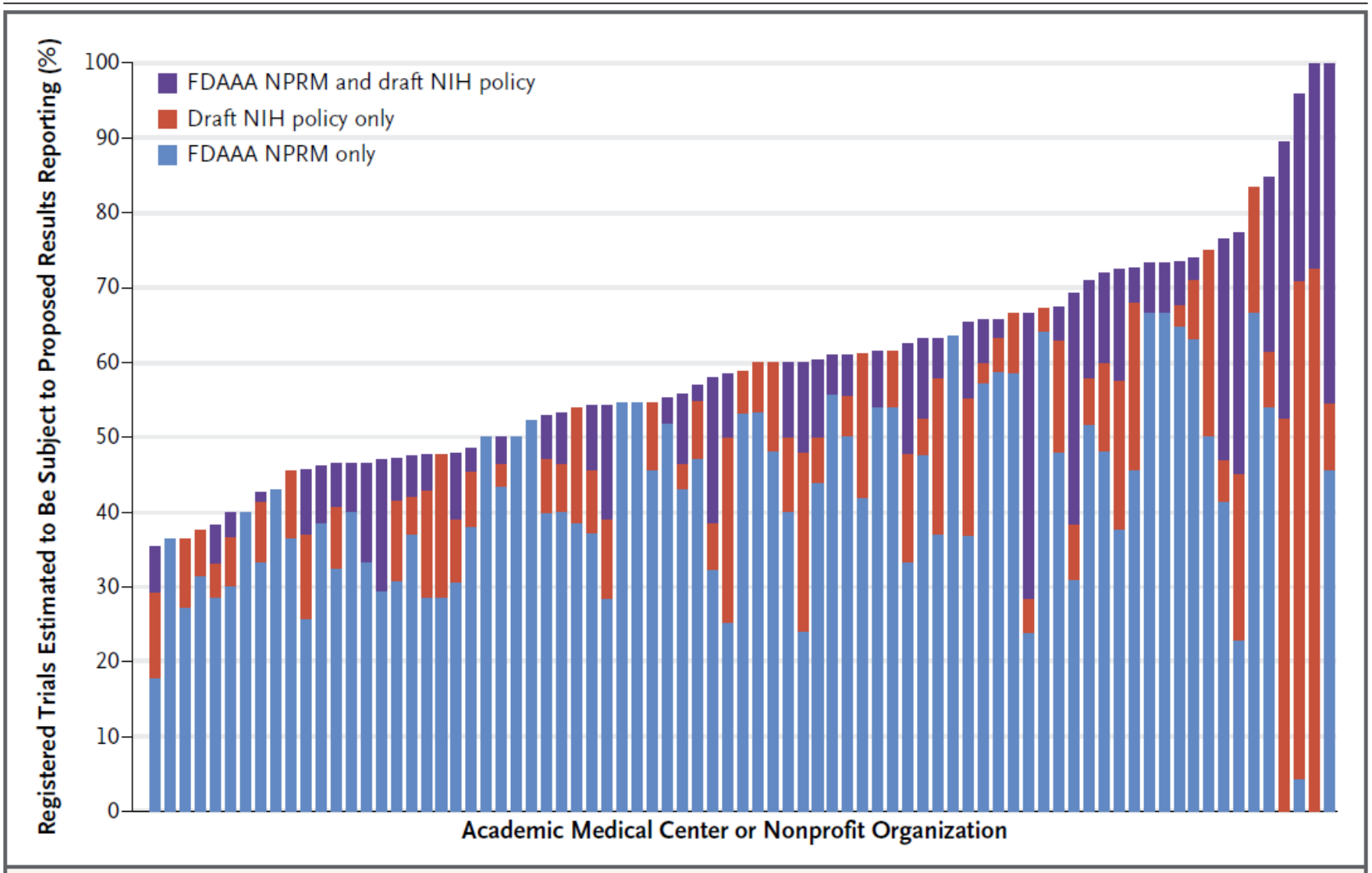


Figure 1. Trials by 80 Sponsors Estimated to Be Subject to Proposed Results Reporting.

Zarin DA, Tse T, Ross JS. *N Engl J Med*. 2015 May 20.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

The ClinicalTrials.gov Results Database — Update and Key Issues

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., Robert M. Califf, M.D., and Nicholas C. Ide, M.S.

ABSTRACT

BACKGROUND

The ClinicalTrials.gov trial registry was expanded in 2008 to include a database for reporting summary results. We summarize the structure and contents of the results database, provide an update of relevant policies, and show how the data can be used to gain insight into the state of clinical research.

METHODS

We analyzed ClinicalTrials.gov data that were publicly available between September 2009 and September 2010.

RESULTS

As of September 27, 2010, ClinicalTrials.gov received approximately 330 new and 2000 revised registrations each week, along with 30 new and 80 revised results submissions. We characterized the 79,413 registry and 2178 results of trial records available as of September 2010. From a sample cohort of results records, 78 of 150 (52%) had associated publications within 2 years after posting. Of results records available publicly, 20% reported more than two primary outcome measures and 5% reported more than five. Of a sample of 100 registry record outcome measures, 61% lacked specificity in describing the metric used in the planned analysis. In a sample of 700 results records, the mean number of different analysis populations per study group was 2.5 (median, 1; range, 1 to 25). Of these trials, 24% reported results for 90% or less of their participants.

CONCLUSIONS

ClinicalTrials.gov provides access to study results not otherwise available to the public. Although the database allows examination of various aspects of ongoing and completed clinical trials, its ultimate usefulness depends on the research community to submit accurate, informative data.

Source: *N Engl J Med* 2011; 364:852-860

ClinicalTrials.gov

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.”

Full Text View | Tabular View | Study Results | Related Studies

Brief Descriptive Title of Clinical Trial

Study Recruitment Status

Information provided by Organization

Study Type:	Interventional
Study Design:	Randomized, Double Masked, Placebo Control, Parallel Assignment
Interventions:	Drug: Drug A; Drug: Drug B

▶ Participant Flow

Recruitment Details – Key information relevant to the recruitment process for the overall study, such as dates of the recruitment.

Pre-Assignment Detail – Significant events and approaches for the overall study following participant enrollment, but prior to assignment.

Overall Study

	Drug A	Drug B	Placebo
STARTED			
COMPLETED			
Not Completed			
Lost to Follow-up			
Adverse Event			

▶ Baseline Characteristics

	Drug A	Drug B	Placebo	Total
Number of Participants				
Age				
Gender				
Female				
Male				

▶ Outcome Measures

Primary Outcome Measure

Measure Name	
Measure Description	
Time Frame	

Population Description – Explanation of how the number of participants for analysis was determined.

Measured Values

	Drug A	Drug B	Placebo
Number of Subjects			
Primary Outcome Measure			

Statistical Analysis for Primary Outcome Measure

Groups	
Method	
P-Value	
Mean Difference	
95% Confidence Interval	

Additional Details About the Analysis – e.g., null hypothesis, power calculation, and whether the p-value is adjusted for multiple comparisons

▶ More Information

Certain Agreements – Information about restrictions on the ability of the principal investigator to disseminate trial data after trial completion

Limitations and Caveats – Limitations of the study, such as early termination leading to small numbers of subjects analyzed

Results Point of Contact – Phone and/or email for additional information about the results

4 Scientific Modules

- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Adverse Events

Administrative Information
e.g., “Certain Agreements”

Question: Which parts would you NOT need to write a journal article?

- Baseline Characteristics
  - One table, for each arm and overall
  - Age (continuous or categorical)
  - Gender
- Participant Flow
  - # Started and # completed each arm
- Outcome Measures
  - Summary data for each prespecified Primary and Secondary Outcome Measure (per arm)
- Adverse Events
  - Table of all Serious Adverse Events (per arm)
  - Table of "other" Adverse Events that occur in more than 5% of participants (per arm)

What Does QA Address?

- Tables should convey study design, conduct, and analysis
- Data must make sense
  - Measure name, units, and data must match
  - Use words precisely (e.g., incidence, rate)
  - No invalid entries
    - E.g., 823 hours/day; “time to survival”
  - No missing parameters or data
- Results record must be logical and internally consistent

We Have Observed 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)

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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?

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PLOS | MEDICINE

Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals

Carolina Riveros[1,2,3], Agnes Dechartres[1,2,3]*, Elodie Perrodeau[1,3], Romana Haneef[1,3], Isabelle Boutron[1,2,3,4], Philippe Ravaud[1,2,3,4,5]

1 INSERM U738, Paris, France, **2** Université Paris Descartes—Sorbonne Paris Cité, Paris, France, **3** Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France, **4** French Cochrane Centre, Paris, France, **5** Mailman School of Public Health, Columbia University, New York, New York, United States of America

Abstract

Background: The US Food and Drug Administration Amendments Act requires results from clinical trials of Food and Drug Administration–approved drugs to be posted at ClinicalTrials.gov within 1 y after trial completion. We compared the timing and completeness of results of drug trials posted at ClinicalTrials.gov and published in journals.

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"**Conclusions**: Our results highlight the need to search ClinicalTrials.gov for both unpublished and published trials. **Trial results, especially serious adverse events, are more completely reported at ClinicalTrials.gov than in the published article**."

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

ABSTRACT

BACKGROUND

Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA–LAMA regimen in these patients is unclear.

METHODS

We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 μg) plus the LAMA glycopyrronium (50 μg) once daily or the LABA salmeterol (50 μg) plus the inhaled glucocorticoid fluticasone (500 μg) twice daily. The primary outcome was the annual rate of all COPD exacerbations.

RESULTS

A total of 1680 patients were assigned to the indacaterol–glycopyrronium group, and 1682 to the salmeterol–fluticasone group. Indacaterol–glycopyrronium showed not only noninferiority but also superiority to salmeterol–fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003). The indacaterol–glycopyrronium group

Source: Wedzicha JA, et al. *N Engl J Med*. 2016 Jun 9;374(23):2222-34.

Wedzicha et al. (2016) online at www.nejm.org

Online publication of a *NEJM* original article reporting the results of the FLAME Trial (NCT01782326) explicitly linked to results information posted on ClinicalTrials.gov:

> "The protocol includes a list of 27 secondary outcome measures; we report data for 19 of these outcomes here and in Sections 4 and 5 in the Supplementary Appendix. **The outcomes for which data are not reported herein can be found at ClinicalTrials.gov** (https://clinicaltrials.gov/ct2/show/results/NCT01782326)."

ClinicalTrials.gov

Source:

The NE
JOUR

HOME | ARTICLES & MULTIMEDIA

ORIGINAL ARTICLE

Indacaterol–Glycopyr
COPD

Jadwiga A. Wedzicha, M.D., Donald Ban
Roche, M.D., R. Timothy Ayers, M.Sc., C
Vogelmeier, M.D., for the FLAME Investig
N Engl J Med 2016; 374:2222-2234 | Jun

Abstract | Article | References

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exacerbations.

The protocol includes a list of 27
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exacerbation and the annual rate
exacerbations. We also assessed
from 0 to 12 hours (in a subgroup
George's Respiratory Questionna
with higher scores indicating wors
4 points, as compared with the score with placebo[24]), and the use of rescue medication.

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

QVA vs. Salmeterol/Fluticasone, 52-week Exacerbation Study, FLAME (EFfect of Indacaterol Glycopyronium Vs Fluticasone Salmeterol on COPD Exacerbations)

This study has been completed.

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01782326

First received: January 30, 2013
Last updated: May 5, 2016
Last verified: May 2016
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Results First Received: May 4, 2016

Measured Values

	QVA149	Long Acting B2 Agonist (LABA) and Inhaled Corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1528	1556
Rate of COPD Exacerbations [units: COPD Exacerbations/year] Least Squares Mean (95% Confidence Interval)	3.59 (3.28 to 3.94)	4.03 (3.68 to 4.41)

Statistical Analysis 1 for Rate of COPD Exacerbations

Groups [1]	All groups
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	Generalized linear model
Rate Ratio [4]	0.89
95% Confidence Interval	0.83 to 0.96

Implications of New QC Posting Practices – 2 NCI Case Studies

NCT00060528 – Pre-QC Review

- Outcome Measure
  - Title: “Immune Response”
  - Description: “…an enhanced PSA-specific T-cell immune response greater than or equal to…”
- Arm Information
  - Number of Arms: “1”
  - Arm Title: “Phase 2”
  - Arm Description: “Phase 2 patients are randomized among **4 arms**…”

	Phase 2
Number of Participants Analyzed	32

	Phase 2
Immune Response [units: Participants]	29

ClinicalTrials.gov

NCT00060528 – Post-QC Review

Arm/Group Title	No GM	Rec-hGM	rF-GM (10^7pfu),	rF-GM (10^8)
▼ Arm/Group Description:	Vaccine subcutaneously with no GM	Vaccine subcutaneously with Rec-hGM sucutaneously (daily x 4/vaccine)	Vaccine subcutaneously with rF-GM (10^7pfu) subcutaneously x1	Vaccine subcutaneously with rF-GM (10^8) subcutaneously x1
Number of Participants Analyzed	8	6	7	8
Measure Type: Number Units: Participants	2	4	4	3

NCT00082017 – Pre-QC Review

- Outcome Measure
  - Title: “Clinical Response Rate”
  - Description: “…the **percentage of participants** with a response addressed by the International Workshop to…”

	UCN-01 for T-cell Lymphomas - Cohort 1 Every 28 Days	UCN-01 for T-cell Lymphomas - Cohort 2 Every 21 Days
Number of Participants Analyzed	11	9
Clinical Response Rate [units: Percentage of participants]		
Complete response	18	0
Complete response unconfirmed	0	0
Partial response	9	0
Progressive disease	54	4

ClinicalTrials.gov

NCT00082017 – Post-QC Review

Arm/Group Title	UCN-01 for T-cell Lymphomas - Cohort 1 Every 28 Days	UCN-01 for T-cell Lymphomas - Cohort 2 Every 21 Days
▼ Arm/Group Description:	Cycle 1: 45 mg/m^2/day continuous intravenous infusion 1 to 3 days (72 hours) for total dose of 135 mg/m^2 Cycle 2: 45 mg/m^2/day continuous intravenous infusion 1 to 2 days (36 hours) for total dose of 68 mg/m^2. Repeat cycles every 28 days.	Cycle 1: 45 mg/m^2/day continuous intravenous infusion 1 to 3 days (72 hours) for total dose of 135 mg/m^2 Cycle 2: 45 mg/m^2/day continuous intravenous infusion 1 to 2 days (36 hours) for total dose of 68 mg/m^2; Repeat cycles every 21 days.
Number of Participants Analyzed	11	9
Measure Type: Number Units: Percentage of participants		
Complete response	18	0
Complete response unconfirmed	0	0
Partial response	9	0
Progressive disease	55	45
Stable disease	9	33
Not evaluable	9	22

What is our Goal?

1. Make it as straightforward as possible for the motivated person with the requisite knowledge to enter results
2. Make it as clear as possible what the requisite knowledge is:
   a) Clinical research knowledge and skills
   b) Understanding of specific trial, and access to summary data

ClinicalTrials.gov

Upgrades from ClinicalTrials.gov

- User-focused improvements to data entry system
- 12 PhD level quality reviewers are available for 1:1 assistance at any stage in process
  - "navigator" process available to walk you through complete data entry
- Reports within the system to help organizational administrators keep track of the status of their records
- Email and other warning system in place to alert Responsible Parties when there are problems that require attention

Requesting One-on-One Help with Results

ClinicalTrials.gov

Reactions to 1-to-1 Results Navigation

- "The session with clinicaltrials.gov was highly effective, and indeed we worked out methods for reporting side effects for crossover studies."
- "I've been very impressed with how responsive the PRS team has been with my questions. Additionally, the quality and completeness of the answers has been fantastic."
- "We so appreciate the time and the discussion yesterday and especially your continued interest in helping us seek the best possible resolution with our challenges with the results section of this study."
- "Thank you so much for your clear explanation. It helps me a lot."
- "I cannot thank you enough for helping me work through this. … I have learned a lot, and have saved all the informational links for future use with the site."

ClinicalTrials.gov

Heard on the Street:

- "You only have to register **if** you're planning to publish…"
- "We never planned to analyze those data [arm]…"
- "FDAAA will never be enforced…"
- "All of our investigators publish…"
- "Some studies aren't designed to produce meaningful results, so it would be misleading."
- "You ask for data that we don't have…"
- "We don't have enough statistical help…"
- "The data are archived…"
- "We can't afford to support this effort…"

FDAAA "Basic" Results Reporting by NCI Sponsored and NCI Funded

All data as of 11/1/2016

	# of Registered pACTs	# Registered Trials ("pACTs") That May Need Results		% Reporting Results
		Total*	Reporting Results**	
NCI--sponsor	1,035	652	601	92%
Other NCI funded	2,690	1,609	711	44%

*Total = [Non-phase 0/1 interventional studies AND (IND or IDE OR a drug, biologic, or device AND at least one US site) AND completed after December 2007] AND [Primary Completion Date ≥ 1 Year]

**Reporting Results = Trials for which summary results are posted or submitted to ClinicalTrials.gov OR delayed submission of results are acceptable (i.e. submission of a certification or an extension request)

FDAAA "Basic" Results Reporting by Top 10 NIH Grant Recipients (FY2014)

Sponsor Rank	# Registered Trials ("pACTs") That May Need Results		% Reporting Results
	Total	Reporting Results	
1	106	24	23%
2	103	80	78%
3	136	20	15%
4	102	35	34%
5	102	90	**88%**
6	87	36	41%
7	43	28	65%
8	97	23	24%
9	59	12	20%
10	138	12	**9%**

STAT News – December 13, 2015

- Assessed whether institutions reported results and whether they were reported "on time"
  - Analysis included trials of unapproved drugs or devices (if a certification was not on file)
- "The worst offenders included four of the top 10 recipients of federal medical research funding from the National Institutes of Health: Stanford, the University of Pennsylvania, the University of Pittsburgh, and the University of California, San Diego."

http://www.statnews.com/2015/12/13/clinical-trials-investigation/

High-level Implications of Recent Policies

- Transparency
  - Traditionally, investigators decided whether, when, and how to report results
  - Current policies promote systematic reporting of trial information
- Accountability
  - Organizations that sponsor studies will be held responsible for their conduct and reporting
    - Requires fundamental changes throughout the CRE: funders, sponsors, investigators
  - Key Message:
    The time to decide if study is worth reporting is BEFORE the participants are put at risk, not AFTER
- Leadership is key!

ClinicalTrials.gov

Final Rule Webinar Series

- Available at: http://clinicaltrials.gov/ct2/manage-recs/present

1. Overview of the Final Rule – effective and compliance dates, applicability of final rule, and results submission for unapproved products
2. Final Rule Clinical Trial Registration Information Submission Requirements - who, when, what, and update requirements
3. Final Rule Clinical Trial Results Information Submission Requirements - who, when, what, update requirements, posting, & quality control

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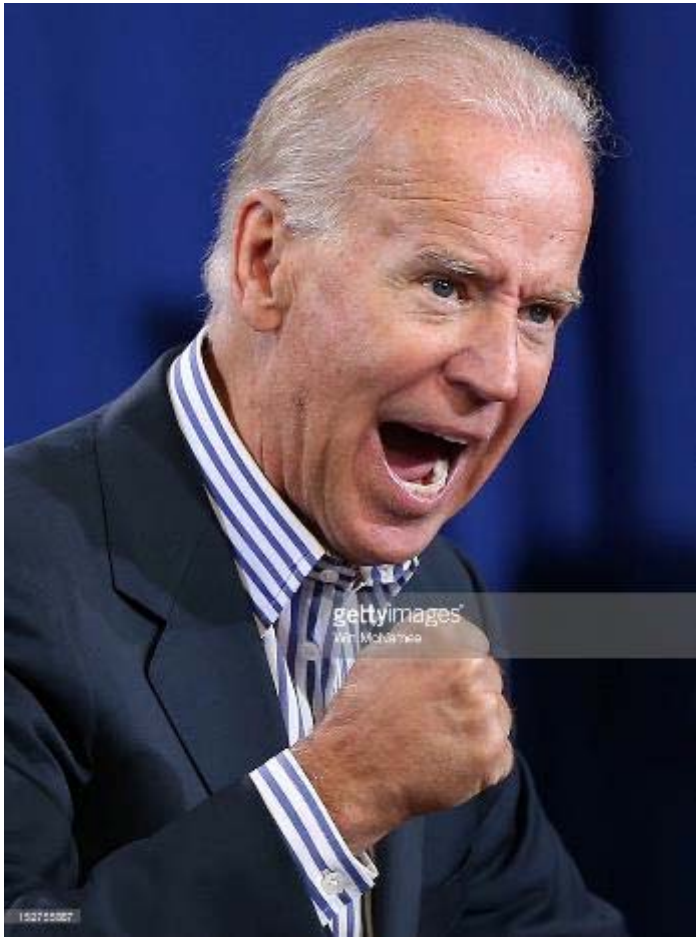

Under the law, it says you must report. If you don't report, the law says you shouldn't get funding. I'm going to find out if it's true [that the research centers aren't reporting the results] and if it's true, I'm going to cut funding. That's a promise.

Vice President Joe Biden
June 29, 2016

Additional Resources

International Committee of Medical Journal Editors (ICMJE) Policy
http://www.icmje.org/publishing_10register.html

HHS Final Rule Clinical Trials Registration and Results Information Submission
https://www.federalregister.gov/d/2016-22129

NIH Policy on the Dissemination of Clinical Trial Information
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

National Cancer Institute (NCI) Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials
http://grants.nih.gov/grants/guide/notice-files/NOT-CA-15-

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Additional Resources (cont.)

Contact us: register@clinicaltrials.gov

ClinicalTrials.gov information (Submit Studies page)
http://clinicaltrials.gov/ct2/manage-recs

Office of Extramural Research (OER)
http://grants.nih.gov/Clinicaltrials_fdaaa/

Food and Drug Administration (FDA)
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm

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Select Publications

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

Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. N Engl J Med; 2016 Sept 16.

Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. JAMA; 2016 Oct 4;316(13):1353-1354.

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

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

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