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ClinicalTrials.gov

Federal Demonstration Partnership Meeting – September 2018

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National Library of Medicine

NIH U.S. National Library of Medicine

https://ClinicalTrials.gov

Topics

- Background and Overview
- Implementation of 42 CFR Part 11
- NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
- Revised Common Rule Informed Consent posting requirements
- 21st Century Cures Act
- Information quality improvement efforts
- International Committee of Medical Journal Editors (ICMJE) Policy on Data Sharing Statements

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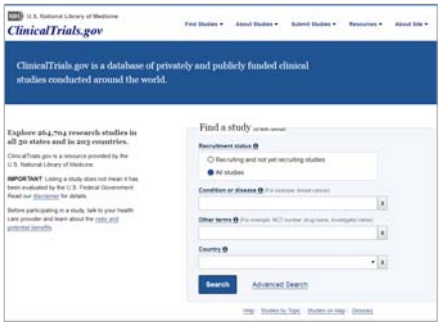
About ClinicalTrials.gov

- Clinical studies registry and results database
  - Over 280,000 records (interventional & observational studies & expanded access information)
  - Studies with locations in 50 states and over 200 countries
  - Privately and publicly funded studies involving human subjects
  - Study information submitted by sponsor or principal investigator
- Website and registry launched in February 2000
  - Results database launched September 2008
  - Over 32,000 studies with summary results
- Database updated nightly
- Usage
  - 171 million page views per month
  - 93,000 unique visitors per day



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Brief History - Select U.S. Laws and Policies

- **1997 Food and Drug Administration Modernization Act (FDAMA)**
- 2000 ClinicalTrials.gov launched
- **2005 International Committee of Medical Journal Editors (ICMJE)**
- **2007 Food and Drug Administration Amendments Act (FDAAA)**
- 2008 FDAAA results submission requirements start
- 2013 Centers for Medicare & Medicaid Services (CMS)
- 2014 FDAAA Notice of Proposed Rulemaking (NPRM) and National Institutes of Health (NIH) Policy Proposal
- **2016 Final Rule for FDAAA (42 CFR Part 11) and NIH Policy on Dissemination of Clinical Trial Information**

https://clinicaltrials.gov/ct/manage-recs/resources

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Public Benefits of Access to Clinical Trial Information

- Meet ethical obligation to human subjects (e.g., that results will be used to help others)
- Inform future research and research funding decisions
- Mitigate information bias (e.g., non-publication)
- Evaluate research integrity (e.g., adherence to protocol)
- Prevent duplication of trials of unsafe or ineffective interventions
- Provide access to data to support evidence-based medicine
- Enhance patient access to enrollment in clinical trials

All contribute to increased public trust in clinical research

Why Register and Report Results?

- **Required by most medical journals (ICMJE)**
  - Registration for all clinical trials (all interventions) and encourage results reporting, even if not required by law
- **Federal law (FDAAA 801) and regulations (42 CFR Part 11)**
  - Registration & results submission for "applicable clinical trials"
  - Federal law in effect since September 2007; regulations effective January 18, 2017 and compliance date April 18, 2017
- **Expectation for NIH-supported clinical trials**
  - Registration & results submission, even if not subject to FDAAA 801
  - Policy effective January 18, 2017

ICMJE = International Committee of Medical Journal Editors; FDAAA 801 = Section 801 of the Food and Drug Administration Amendments Act of 2007; NIH = National Institutes of Health

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Many "local" policies

- Know your funder's and organization's requirements!
- Example: Department of Veterans Affairs
  - "In support of the VHA health care mission and in keeping with the Office of Research and Development's (ORD) commitment to improve veterans' access to clinical trials, all clinical trials that ORD sponsors are registered with the National Library of Medicine's (NLM) public registry, ClinicalTrials.gov."
  - "VA investigators …. must have their clinical trial registered before funding will be released and prior to enrolling participants into their study."

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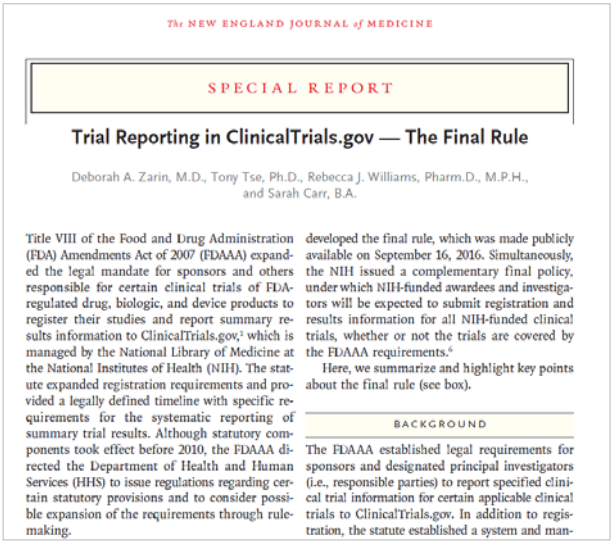
http://www.research.va.gov/resources/ORD_Admin/clinical_trials/

Overview of the Final Rule (42 CFR Part 11)



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 rule-making.

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-

- Clarifies terms and provisions in the statute (FDAAA)
  - ACT determination approach
- Expands basic requirements
  - Results information required for ACTs of unapproved products
  - Full protocol and statistical analysis plan required with results (will be made public)
- Other Issues
  - Narrative summaries not required

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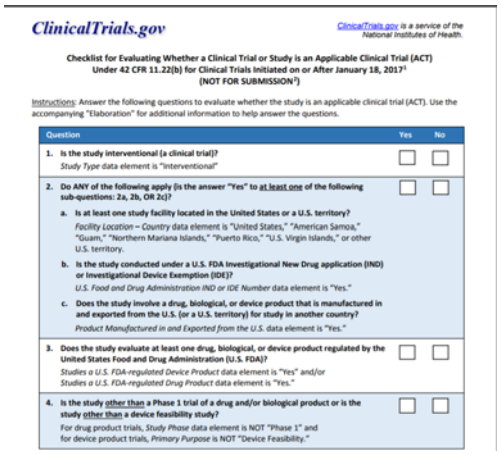
Zarin et al. N Engl J Med; 2016 Sept 16.

42 CFR Part 11: Applicable Clinical Trial

Applicable Clinical Trial

- Interventional study (clinical trial)*
- Studies a drug, biologic, or device product regulated by the U.S. FDA (at least one of the following):
  - Site in the U.S. (or U.S. territory); or
  - Study conducted under an IND/IDE; or
  - Product manufactured in and exported from the U.S. for study in another country
- Not Phase 1 trial (drug or biologic) or a small feasibility study (device)

ACT Checklist and Elaboration



ClinicalTrials.gov

ClinicalTrials.gov is a service of the National Institutes of Health.

Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) Under 42 CFR 11.22(b) for Clinical Trials Initiated on or After January 18, 2017[1] (NOT FOR SUBMISSION[2])

Instructions: Answer the following questions to evaluate whether the study is an applicable clinical trial (ACT). Use the accompanying "Elaboration" for additional information to help answer the questions.

Question	Yes	No
1. **Is the study interventional (a clinical trial)?** *Study Type* data element is "Interventional"	☐	☐
2. **Do ANY of the following apply (is the answer "Yes" to at least one of the following sub-questions: 2a, 2b, OR 2c)?**	☐	☐
a. **Is at least one study facility located in the United States or a U.S. territory?** *Facility Location – Country* data element is "United States," "American Samoa," "Guam," "Northern Mariana Islands," "Puerto Rico," "U.S. Virgin Islands," or other U.S. territory.		
b. **Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)?** *U.S. Food and Drug Administration IND or IDE Number* data element is "Yes."		
c. **Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country?** *Product Manufactured in and Exported from the U.S.* data element is "Yes."		
3. **Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)?** *Studies a U.S. FDA-regulated Device Product* data element is "Yes" and/or *Studies a U.S. FDA-regulated Drug Product* data element is "Yes."	☐	☐
4. **Is the study other than a Phase 1 trial of a drug and/or biological product or is the study other than a device feasibility study?** For drug product trials, *Study Phase* data element is NOT "Phase 1" and for device product trials, *Primary Purpose* is NOT "Device Feasibility."	☐	☐

* If the study is a pediatric postmarket surveillance of a device product as required by FDA under Section 522 of the Federal Food, Drug, and Cosmetic Act, it meets the definition of an applicable device clinical trial (42 CFR 11.22(b))
IND = Investigational New Drug application; IDE = Investigational Device Exemption

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42 CFR Part 11: General Requirements

The Responsible Party for an Applicable Clinical Trial (ACT) must:

1. **Register** the trial in ClinicalTrials.gov no later than 21 days after enrollment of the first participant
2. **Update** the trial in ClinicalTrials.gov at least once every 12 months (some information within 15 or 30 days of change*)
3. **Submit summary results** (including adverse events) for certain trials not later than 1 year after the trial's Primary Completion Date
   - Delays allowed in some circumstances

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Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11); update requirements described in 42 CFR 11.64*

General Requirements - NIH Policy

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

- NIH-funded awardees and investigators expected to submit the same registration and results information in the same timeframes as those subject to the statute and rule [42 CFR Part 11]
- Applies to grant and contract applications for funding submitted on or after January 18, 2017 that request support for the conduct of a clinical trial that is initiated on or after January 18, 2017

Recent Developments

- July 20, 2018: Delayed Enforcement and Short-Term Flexibilities for Some Requirements Affecting Prospective Basic Science Studies Involving Human Participants (NOT-OD-18-212)
- August 10, 2018: Request for Information (RFI): Registration and Results Reporting Standards for Prospective Basic Science Studies Involving Human Participants (NOT-OD-18-217)
  - NIH seeks comments, including on specific examples of studies that pose the greatest challenges in meeting ClinicalTrials.gov requirements and specific reasons for challenges
  - Comments due by November 12, 2018

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https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

ClinicalTrials.gov Study Record
(one record per trial – assigned a unique NCT #)

- **Registration section**
  - Submitted at trial initiation
  - Summarizes trial protocol, e.g.,
    - Condition(s)
    - Interventions
    - Study Design
    - Outcome Measures
  - Includes recruitment information
    - Eligibility criteria, study locations, contact information
  - Secondary IDs, including NIH grant or other funding numbers
- **Results section**
  - Submitted after trial completion
  - Summarizes trial results
    - Participant flow
    - Baseline characteristics
    - Primary and secondary outcome measures (including statistical analyses)
    - Adverse events
  - Full protocol and statistical analysis plan (trials with Primary Completion Date ≥ Jan 18, 2017)

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General Results Clarifications

- Summary results at the end of the trial
  - No interim or "real-time" reporting
  - No participant-level reporting
- Summary results submission generally <u>not required</u> for:
  - Registered non-ACTs (e.g., observational studies)
  - Clinical trials completed by December 26, 2007
  - ACTs of products that are not approved as of the Primary Completion Date (PCD), when the PCD is before January 18, 2017 (final rule effective date)
- Relationship to publication (ICMJE)
  - Submitting summary results to ClinicalTrials.gov <u>will not interfere</u> with publication* (but, failing to register the trial will!)

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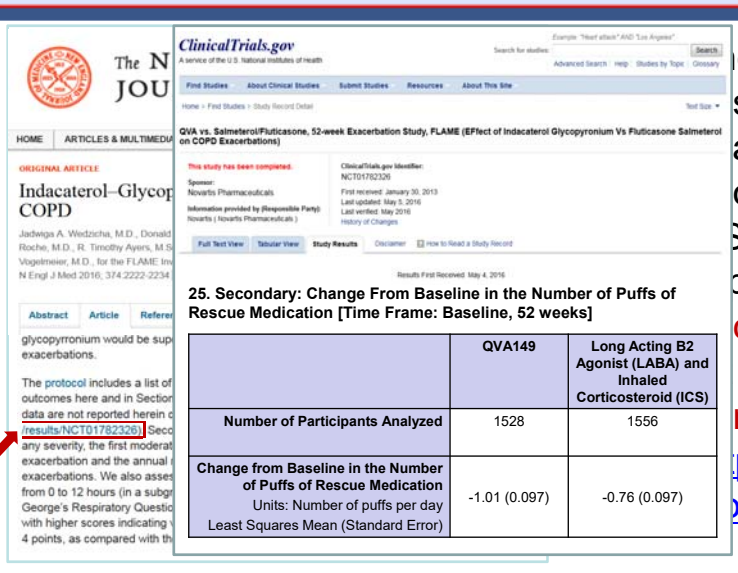
* http://www.icmje.org/publishing_10register.html

Publications and ClinicalTrials.gov Results Information are Complementary



…e protocol includes a list of …secondary outcome …asures; we report data for …of these outcomes here and …Sections 4 and 5 in the …pplementary Appendix. The …comes for which data are … reported herein can be …nd at ClinicalTrials.gov …ps://clinicaltrials.gov/ct2/ …ow/results/NCT01782326)."

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Source: Wedzicha JA, et al. *N Engl J Med*. 2016 Jun 9;374(23):2222-34 and https://clinicaltrials.gov/ct2/show/results/NCT01782326 (adapted).

42 CFR Part 11: Updates and Progress

- Volume continues to increase (first posted 2016 v. 2017)
  - Registration information: 27,809 v. 29,201 (5% increase)
  - Results information: 4,183 v. 5,827 (40% increase)
- Continuing to provide clarification on Final Rule via FAQs and other related content
  - Frequently Asked Questions (FAQs)
  - ACT Checklist and Elaboration document
  - FDAAA 801 and the Final Rule page
- Implementation of key Final Rule provisions
  - Study documents (protocol and statistical analysis plan)
  - QC review criteria and process

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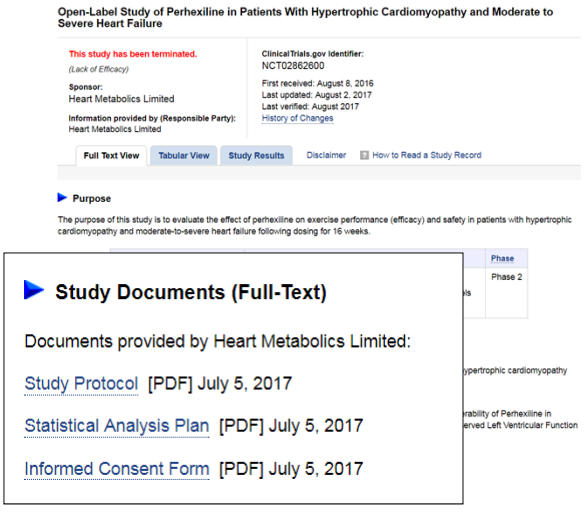
FAQs: https://clinicaltrials.gov/ct2/manage-recs/faq#42CFRPart11; FDAAA 801 and Final Rule: https://clinicaltrials.gov/ct2/manage-recs/fdaaa

Study Documents

- Full Protocol, Statistical Analysis Plan (SAP), and Informed Consent Form may be uploaded to study record at any time
  - Protocol/SAP required with results information if Primary Completion Date is on or after January 18, 2017
  - Informed Consent Form optional (81 FR 64999)
- As of 8/10/2018, nearly 2,100 study records with at least one "document"



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https://clinicaltrials.gov/ct2/show/NCT02862600

Informed Consent Form Revised Common Rule (45 CFR 46.116(h))

- The revised Common Rule requires that for any clinical trial conducted or supported by a Common Rule department or agency, one consent form be posted on a publicly available federal website within a specific time frame
- Federal websites that may be used to satisfy the requirement:
  - ClinicalTrials.gov (for registered clinical trials)
  - Regulations.gov (Docket ID: HHS-OPHS-2018-0021)
- HHS and others are developing instructions and other materials providing more information about this posting requirement
- The compliance date for this provision is January 21, 2019

https://www.regulations.gov/docket?D=HHS-OPHS-2018-0021

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42 CFR Part 11: Potential Consequences of Non-Compliance

- NIH (or other HHS agency) must verify submission of information before releasing any remaining funds for a grant or funds for a future grant and provide opportunity to remedy
- FDA may provide responsible parties with a Notice of Noncompliance and allow 30 days to remedy
- FDA authorized to assess civil monetary penalties up to $10,000/day (amounts adjusted going forward)
- FDA may initiate civil or criminal proceedings
- Notices of non-compliance included in the public record

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Final Rule Section IV. E.1. What are the potential legal consequences of not complying with the requirements of this part? - § 11.66

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."

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

STAT News – January 9, 2018

- Update to 2015 article
  - 72% of required results posted in 2017 v. 58% in 2015
- "… biggest gains were at research institutions singled out for woeful reporting in the earlier STAT investigation…"
  - Memorial Sloan Kettering
  - University of Pittsburgh
  - Stanford University

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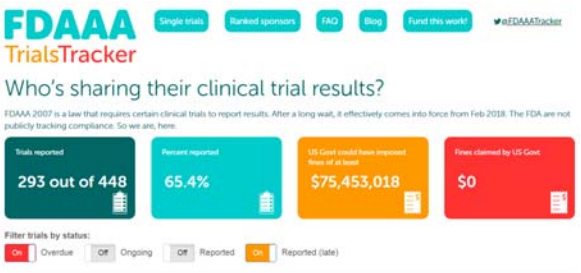
Unreported trial of the week

thebmjopinion

- "Every week, we will publish a brief piece describing one important unreported trial that could be used to improve patient care … Our initial sample of unreported trials will be drawn from those recently breaching the FDA Amendments Act of 2007 (FDAAA)."
- http://blogs.bmj.com/bmj/category/unreported-trial-of-the-week



http://fdaaa.trialstracker.net/

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21st Century Cures Act: Selected ClinicalTrials.gov related provisions

- Section 2052. Compliance Activities Reports (Submit to Congress)
  - Reports on activities to encourage compliance and reports on clinical trials (# of applicable clinical trials, with results, education activities) and actions to enforce compliance
- Section 2053. Updates to Policies to Improve Data
  - For NIH-funded research meeting the definitions of an applicable clinical trial and an NIH-defined Phase III Clinical trial, report results of valid analyses by sex/gender and race/ethnicity in ClinicalTrials.gov (NOT-OD-18-014)
- Section 2054. Consultation
  - Consult with wide range of stakeholders for recommendations on enhancing ClinicalTrials.gov, including with respect to usability, functionality, and search capability
- Section 3032. Expanded access policy
  - Make publicly available expanded access policy and link to the record on ClinicalTrials.gov containing information about the expanded access for such drug

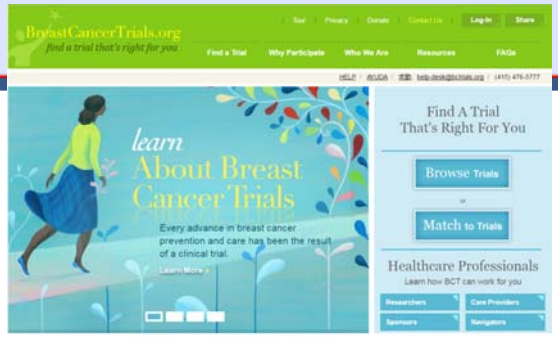
ClinicalTrials.gov Aims

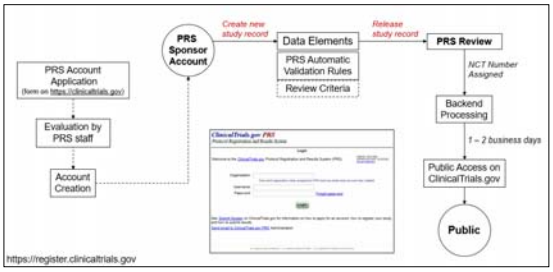
1. Facilitate use of available information

- Enable people to find studies listed on ClinicalTrials.gov
- Allow for re-use of the information (e.g., organizations targeted at specific communities)

2. Provide complete and informative information about clinical studies

- Note: ClinicalTrials.gov does not assess the quality of the study itself, but expects the information describing the study to be clear and complete





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Review Criteria and Examples

- Review Criteria
  - Logic and internal consistency
  - Apparent validity
  - Meaningful entries
  - Formatting
- Major Issue Examples - Outcomes
  - Time to response: 12 participants
  - Time to survival
  - 823 hours of sleep/day
- Sample: 215 results submissions
  - 40% Invalid or inconsistent unit of measure
  - 26% Insufficient information about a scale used for assessment
  - 24% Internal inconsistency
  - 22% Narrative results/conclusions
  - 20% Unclear baseline or outcome measure

Source: Dobbins HD et al. Presented at: Eighth International Congress on Peer Review and Scientific Publication; September 2017; Chicago, IL. http://peerreviewcongress.org/prc17-0383

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Baseline Measure – Major Issue Example

Baseline Measures – Example

	Drug X
GOG Performance Status [units: participants]	
0	48
1	27
2	4

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Baseline Measure – Major Issue Example

Baseline Measures – Example

	Drug X
GOG Performance Status [units: participants]	
0	48
1	27
2	4

Baseline Measures – Example Corrected

	Drug X
Gynecological Oncology Group (GOG) Performance Status [1] [units: participants]	
0 – Fully Active	48
1 – Restricted Strenuous Activity, Ambulatory	27
2 – Ambulatory, Difficulty Walking	4
3 – Limited Self-Care, Partly Confined to Bed	0
4 – Completely Disabled, No Self-Care	0

[1] 5-point, ordinal scale specifying patient's ability to perform activities from 0 (fully active) to 4 (completely disabled, no self-care)

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QC "Success": Industry and Non-Industry Organizations

- Sample evaluated:
  - Initial results submitted on or after January 1, 2017 AND
  - Completed Quality Control (QC) Review on or before April 2, 2018
- $\%\ \text{Success} = \frac{\#\ \text{Records with no Major Issues}}{\#\ \text{Total Record Submissions}} \times 100\%$

		Cycle 1		Cycle 2		Cycles >2	
Org Type	# Orgs	# Records	% Success	# Records	% Success	# Records	% Success
Industry	625	2635	35.03	1114	60.23	387	67.96
Non-Industry	999	4086	20.68	2143	51.10	1077	62.49
All	1624	6721	26.31	3257	54.22	1464	63.93

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Preventing QC Review Issues

- Provide organizations with their own "success" rates; encourage organizations to develop processes to minimize preventable issues
  - Current data indicates heterogeneity among organizations, including high volume submitters
  - Mayo-Wilson et al. reported survey results indicating that academic orgs are dedicating a median (IQR) of 0.08 (0.02–0.25) FTEs to this task
- ClinicalTrials.gov working to help organizations "prevent" quality control review issues. For example:
  - Further evaluation of data submission system (PRS); "just-in-time" support to help users identify and address common major issues prior to submission
  - Additional help documentation; 1-on-1 assistance as needed

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Mayo-Wilson et al. *BMC Medicine.* 2018. 16:60. https://doi.org/10.1186/s12916-018-1042-6

Levels of Transparency

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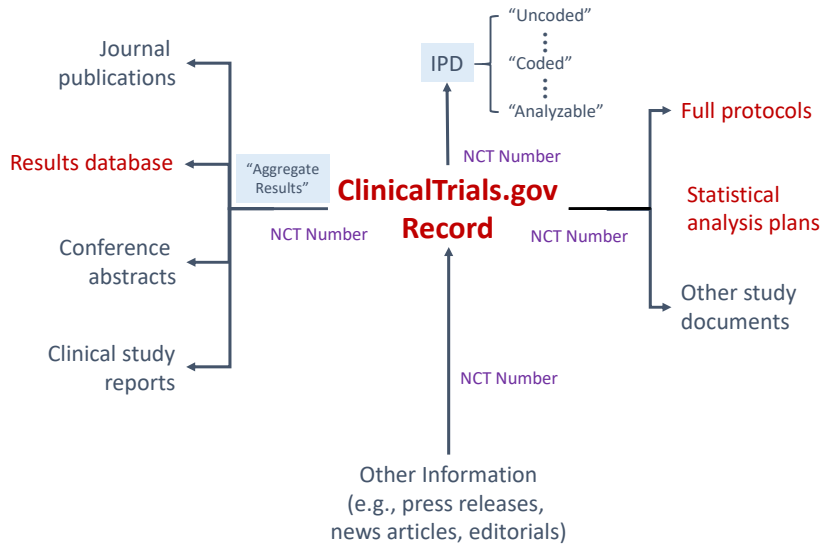
Zarin DA, Tse T. *Science*. 2008.

ICMJE and Data Sharing – June 2017

- ICMJE to require the following as a condition of publication of results of clinical trials
  - Manuscripts must contain a data sharing statement (July 1, 2018)
  - Clinical trial registration must include a data sharing plan (clinical trials that begin enrolling participants on or after January 1, 2019)
    - ClinicalTrials.gov added data elements in June 2017 to provide data sharing statement
    - After study completes, also have data elements to indicate where IPD is shared
- Initial requirements do not yet mandate data sharing
  - Editors may take into consideration data sharing statements when making editorial decisions

Ann Intern Med. doi:10.7326/M17-1028

ClinicalTrials.gov: Information Scaffold



Adapted from Zarin DA, Tse T. PLoS Med 2016;13(1):e1001946.

Tips: Take a Team Approach

- Know funder and regulatory requirements
- Be aware of your institution's approach/SOP
- Work as a team to identify Responsible Party and trials to be reported
  - Sponsored research office, Principal Investigator, Counsel
  - Work across institutions
  - Take actions early to clarify roles and responsibilities
- Create a culture of disclosure

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Tips: Manage Risk Wisely

- Grantee Institutions as Sponsors
  - Standard operating procedures
    - Including addressing when key personnel leave the institution
  - Training
  - Monitor compliance
    - How will you identify and track trials that must be registered and have results submitted?
    - (Some institutions require NCT number for IRB approval)
  - Use personnel and resources appropriately
    - Plan for registration and results reporting early in the trial development process
  - Implement appropriate record retention

NIH Grants FAQs: http://grants.nih.gov/Clinicaltrials_fdaaa/faq.htm

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Public Benefits of Access to Clinical Trial Data

- Meet ethical obligation to human subjects (i.e., that results will be used to help others/inform science)
- Inform future research and research funding decisions
- Mitigate information bias (e.g., non-publication)
- Evaluate research integrity (e.g., adherence to protocol)
- Prevent duplication of trials of unsafe or ineffective interventions
- Provide access to data to support evidence-based medicine
- Enhance patient access to enrollment in clinical trials

All contribute to increased public trust in clinical research

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ClinicalTrials.gov Final Rule Resources

- Final Rule Information Page: https://prsinfo.clinicaltrials.gov
  - Final Rule Webinar Series
  - Applicable Clinical Trial Checklist and Elaboration (ACT Checklist)
  - Frequently Asked Questions
  - Data Element Definitions
  - PRS User's Guide
  - "Coming Soon"
  - NIH FDAAA Update listserv - notification sent to listserv when page updated
- Results submission 1-on-1 assistance – contact us!
  - Email register@clinicaltrials.gov to schedule a teleconference

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-15-011.html

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Additional Resources (cont.)

Contact us: register@clinicaltrials.gov

Final Rule (42 CFR Part 11) Information
https://prsinfo.clinicaltrials.gov

ClinicalTrials.gov Information (Submit Studies page)
https://clinicaltrials.gov/ct2/manage-recs

Office of Extramural Research (OER)
https://grants.nih.gov/policy/clinical-trials.htm

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, Rajakannan T. Update on trial registration 11 years after the ICMJE Policy was established. *N Engl J Med*. 2017 Jan 26;376(4):383-391.

Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. *N Engl J Med*; 2016 Nov 17;375(20):1998-2004.

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 Jun 11;372(24):2371-2.

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Thank you

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National Library of Medicine, National Institutes of Health

Questions? register@clinicaltrials.gov

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