Clinical Trial Reporting Requirements

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Director, ClinicalTrials.gov
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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

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

Many, many “local” policies

- Know your funder’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.”

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

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)

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

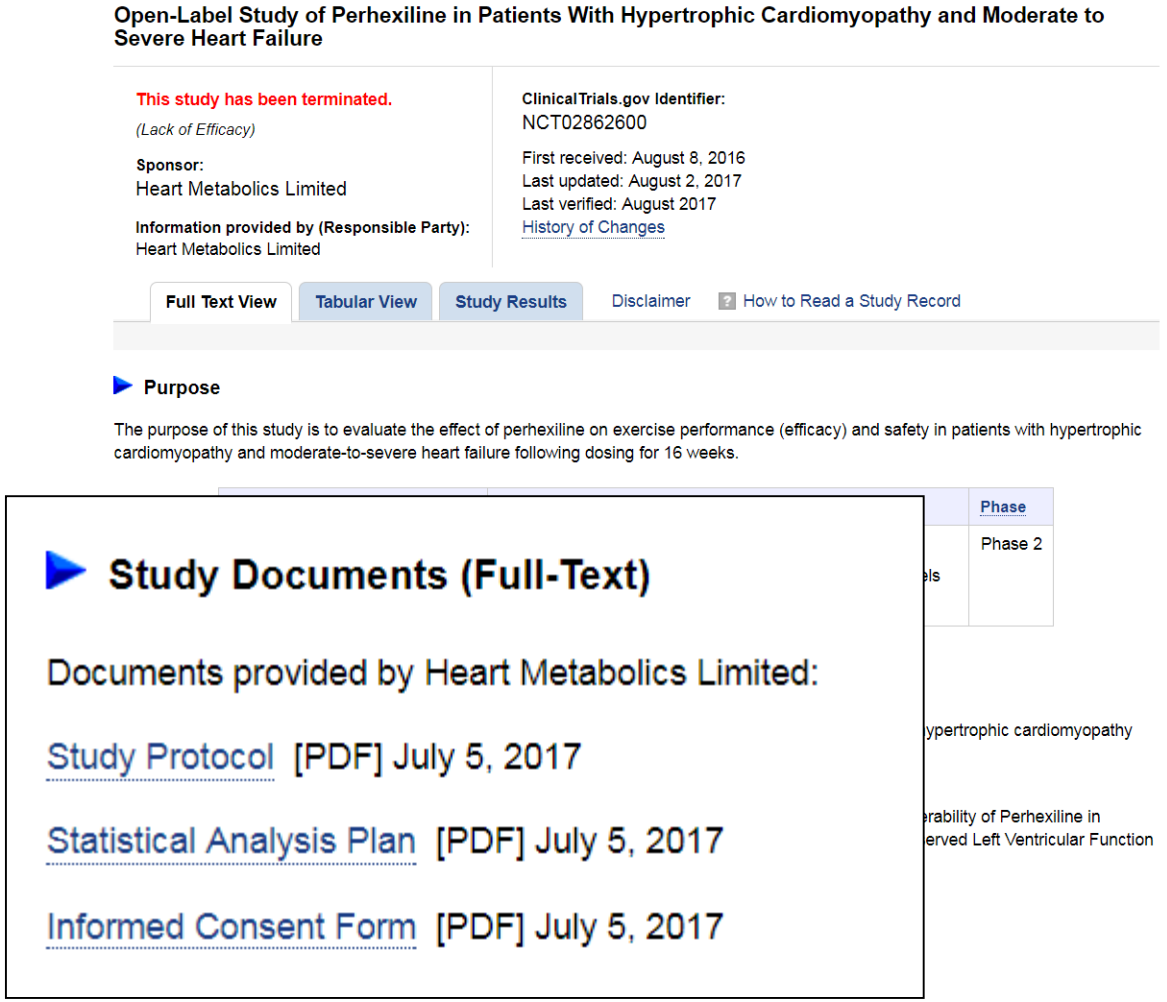
4 Scientific Modules

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

Administrative Information
e.g., “Certain Agreements”

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 2/28/2018, over 930 study records with at least one “document”



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

General Results Clarifications

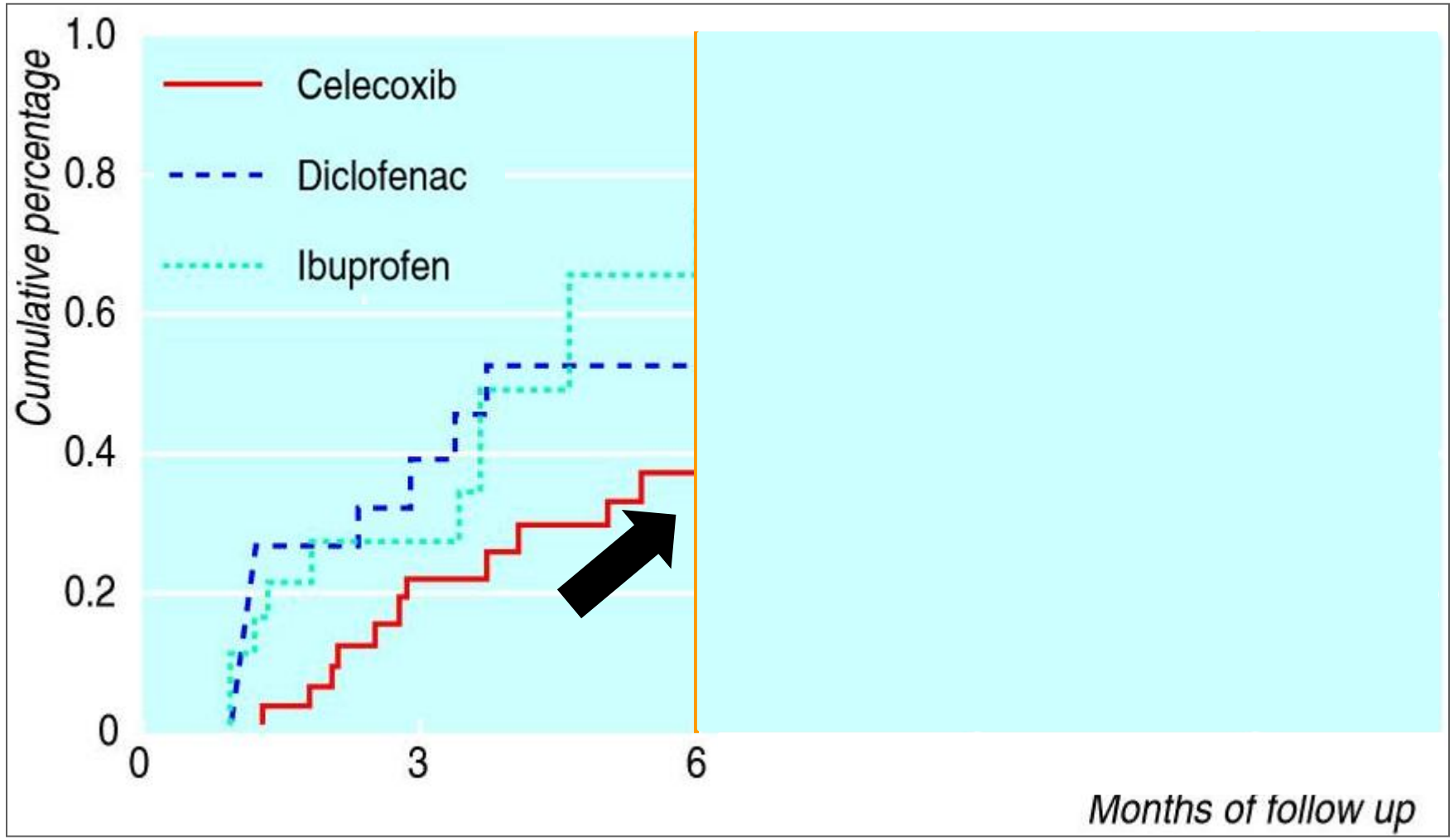
- Summary results at the end of the trial
  - No interim or “real-time” reporting
  - No participant-level reporting
- Summary results submission generally not required for:
  - Registered non-ACTs (e.g., observational studies)
  - Clinical trials completed by December 26, 2007
  - ACTs of products that 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 will not interfere with publication* (but, failing to register the trial will!)

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

What Does QC Address?

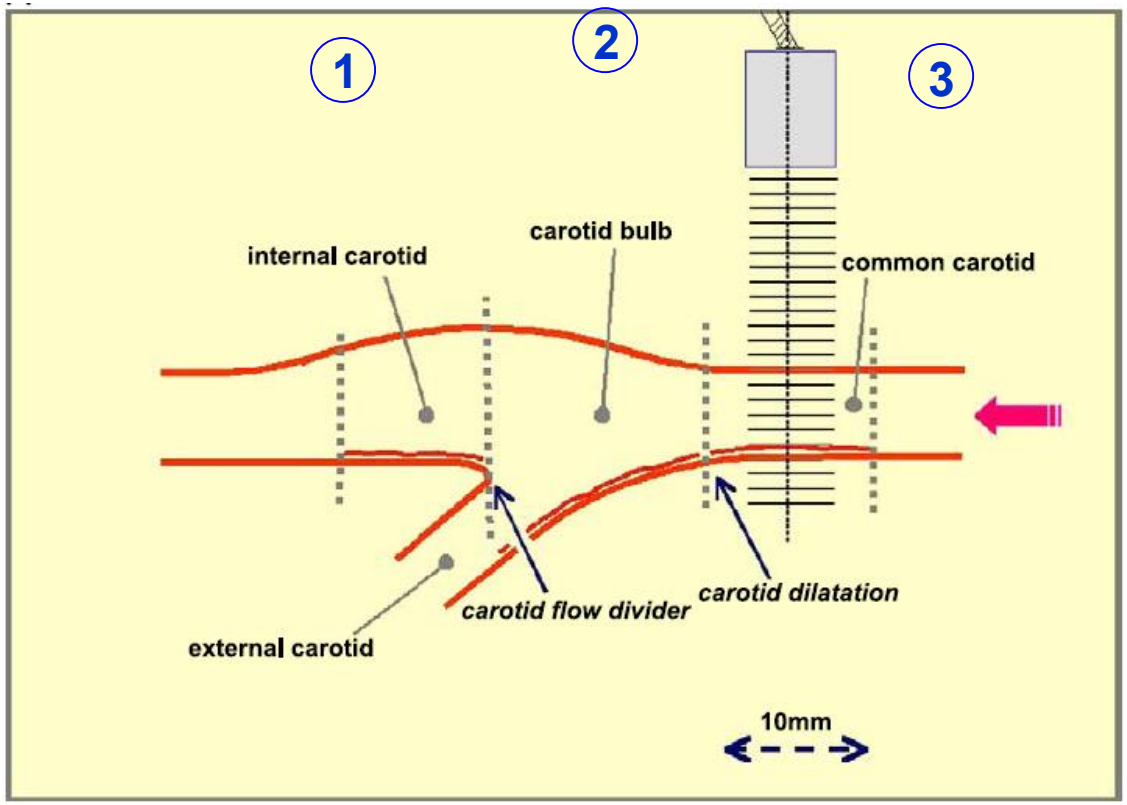
- Each entry must be informative and at required level of specificity
- Data must make sense
  - Measure name, units, and data must match
  - Use words precisely (e.g., incidence, rate)
  - No invalid entries
  - No missing parameters or data
- Results tables should convey study design, conduct, and analysis
- Overall record must be logical and internally consistent

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.



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

ENHANCE (NCT00552097): Prespecified Endpoints

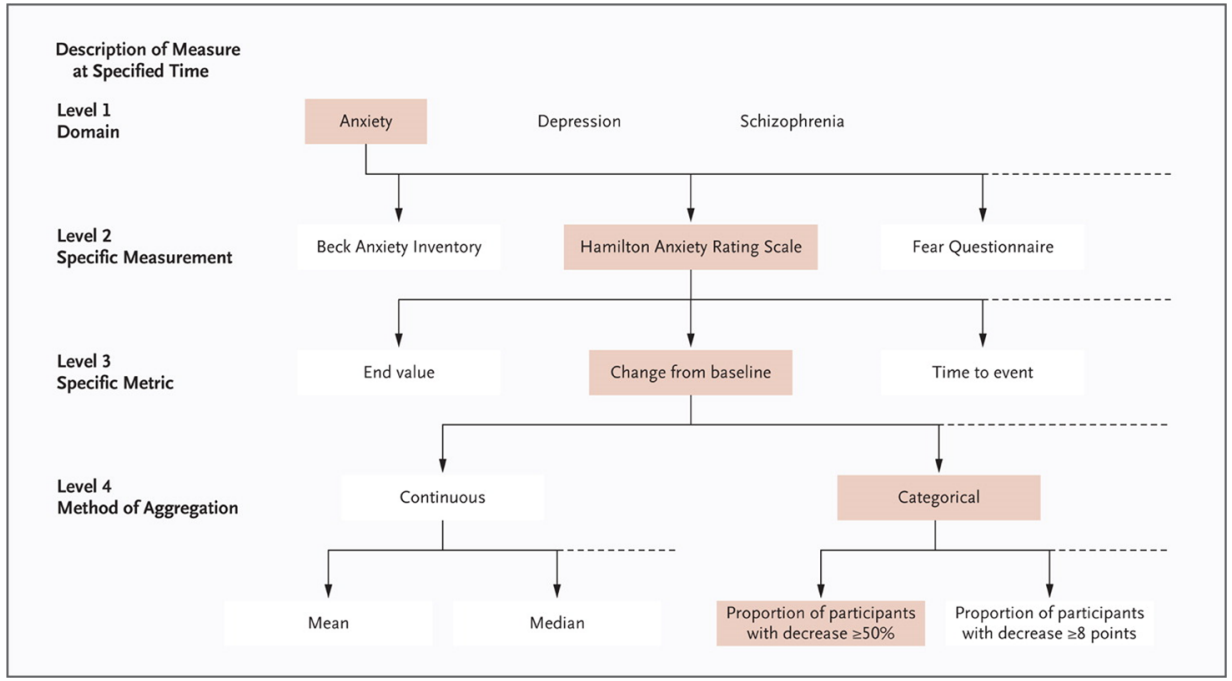


Kastelein JJ et al. *Am Heart J*. 2005 Feb;149(2):234-9.

Major Issues Identified in Registry Submissions

- Most registration issues relate to improper specification of OMs

Example of the 4 Levels of Specification in Reporting Outcome Measures



Source: Zarin DA et al. *N Engl J Med*. 2011;364(9):852-60.

Sample: 215 results submissions

- Invalid or inconsistent unit of measure (40%)
- Insufficient information about a scale used for assessment (26%)
- Internal inconsistency (24%)
- Narrative results/conclusions (22%)
- Unclear baseline or outcome measure (20%)

- **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

Characterizing Major Issues in ClinicalTrials.gov Results Submissions

Major Issue	Number (%) n=471
1. Invalid/inconsistent Unit of Measure	86 (40%)
2. Insufficient information about a scale used for assessment	55 (26%)
3. Internal inconsistency—inconsistency between information in different parts of the record	52 (24%)
4. Written results or conclusions	47 (22%)
5. Unclear Baseline or Outcome Measure	44 (20%)
6. Incorrect Measure Type	23 (11%)
7. "0" Participants at Risk for Adverse Events without explanation	19 (9%)
8. Data with multiple Units of Measure	19 (9%)

1. Invalid Unit of Measure

Title:	Systolic Blood Pressure
Description:	
Time Frame:	6 months

Arm/Group Title	Remuverol Low Dose	Remuverol High Dose
Number Analyzed	2420	2364
Mean (Standard Deviation) Unit of Measure: 142	140 (5)	128 (10)

Suggested edit: "mmHg"

Source: Dobbins HD, et al. Poster at Peer Review Conference. 2017.

Outcome Measure - Error

Title:	Mean Percent Reduction in Percentage of Migraine Days Per 30 Days
Time Frame:	Month 1, Month 4, Month 8

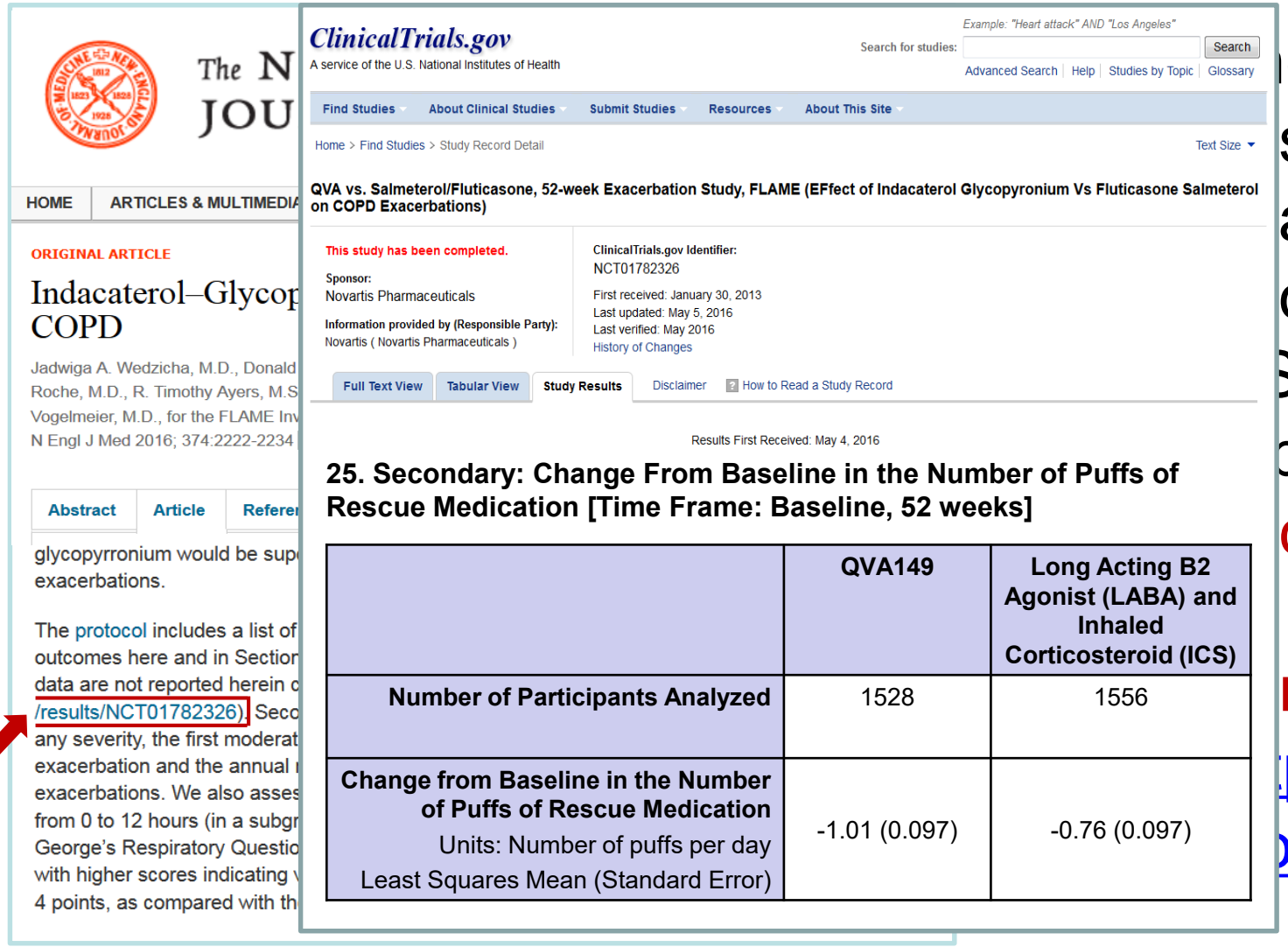
Arm/Group Title	OAT + Beta Blocker (Beta-B)	OAT + BMM + Beta-B
Number of Participants Analyzed	53	69
Median (Standard Deviation) Units: percent	1.5 (0.9)	-6.7 (0.8)

Outcome Measure - Corrected

Title:	Mean Change in Percentage of Migraine Days Per 30 Days
Time Frame:	Month 1 (baseline), Month 4, Month 8

Arm/Group Title	OAT + Beta Blocker (Beta-B)	OAT + BMM + Beta-B
Number of Participants Analyzed	53	69
Mean (Standard Deviation) Units: percentage of 30 days		
Change at Month 4	1.5 (0.9)	-6.7 (0.8)
Change at Month 8	-1.8 (1.6)	-8.1 (1.1)

Publications and ClinicalTrials.gov Results Information are Complementary



The N
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HOME | ARTICLES & MULTIMEDIA

ORIGINAL ARTICLE

Indacaterol–Glycop
COPD

Jadwiga A. Wedzicha, M.D., Donald
Roche, M.D., R. Timothy Ayers, M.S
Vogelmeier, M.D., for the FLAME Inv
N Engl J Med 2016; 374:2222-2234

Abstract | Article | Referer

glycopyrronium would be sup
exacerbations.

The protocol includes a list of
outcomes here and in Section
data are not reported herein c
/results/NCT01782326). Seco
any severity, the first moderat
exacerbation and the annual
exacerbations. We also asses
from 0 to 12 hours (in a subgr
George's Respiratory Questio
with higher scores indicating
4 points, as compared with th

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

25. Secondary: Change From Baseline in the Number of Puffs of Rescue Medication [Time Frame: Baseline, 52 weeks]

	QVA149	Long Acting B2 Agonist (LABA) and Inhaled Corticosteroid (ICS)
Number of Participants Analyzed	1528	1556
Change from Baseline in the Number of Puffs of Rescue Medication Units: Number of puffs per day Least Squares Mean (Standard Error)	-1.01 (0.097)	-0.76 (0.097)

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/
w/results/NCT01782326)."

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).

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

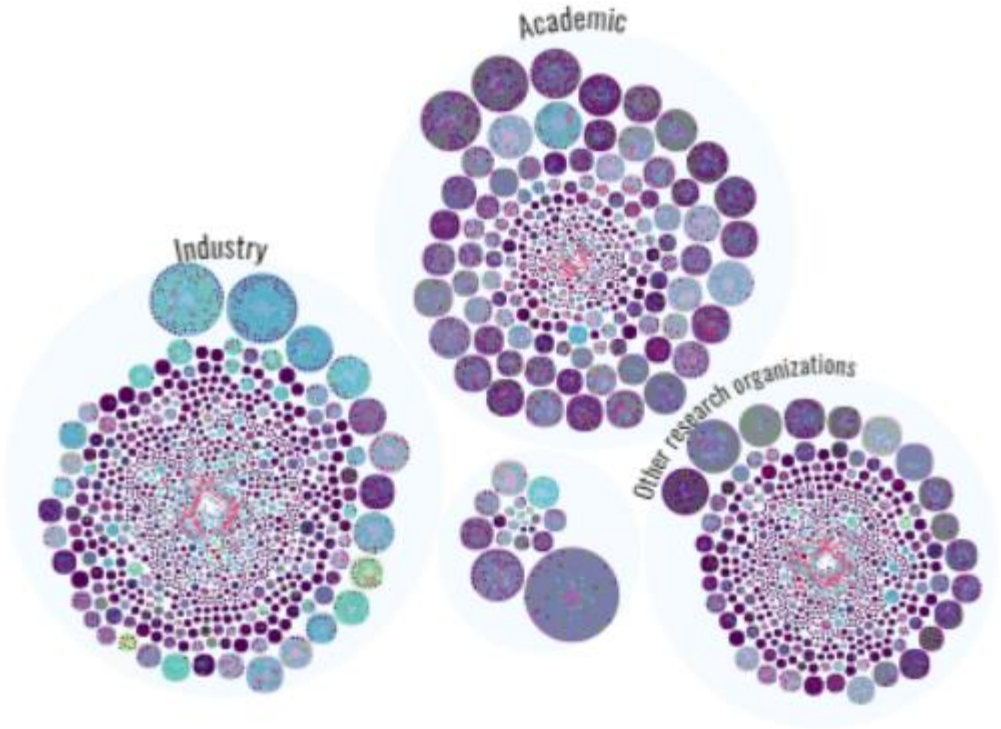
Final Rule Section IV. E.1. What are the potential legal consequences of not complying with the requirements of this part? - § 11.66

STAT News – January 9, 2018

A STAT INVESTIGATION

Faced with public pressure, research institutions step up reporting of clinical trial results

By CHARLES PILLER @cpiller *and* TALIA BRONSHTEIN @ininteraction / JANUARY 9, 2018

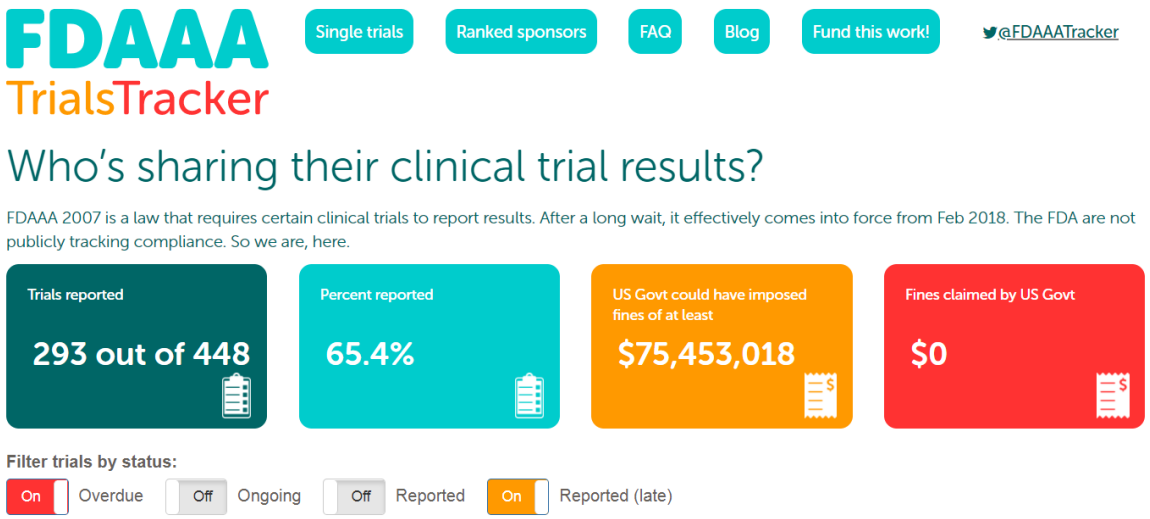


- Update to 2015 article
  - 72% of required results posted in 2017 v. 58% in 2015
- "… biggest gains were at research institutions singled out for woeful reporting in the earlier STAT investigation…"
  - Memorial Sloan Kettering
  - University of Pittsburgh
  - Stanford University

Unreported trial of the week

thebmjopinion

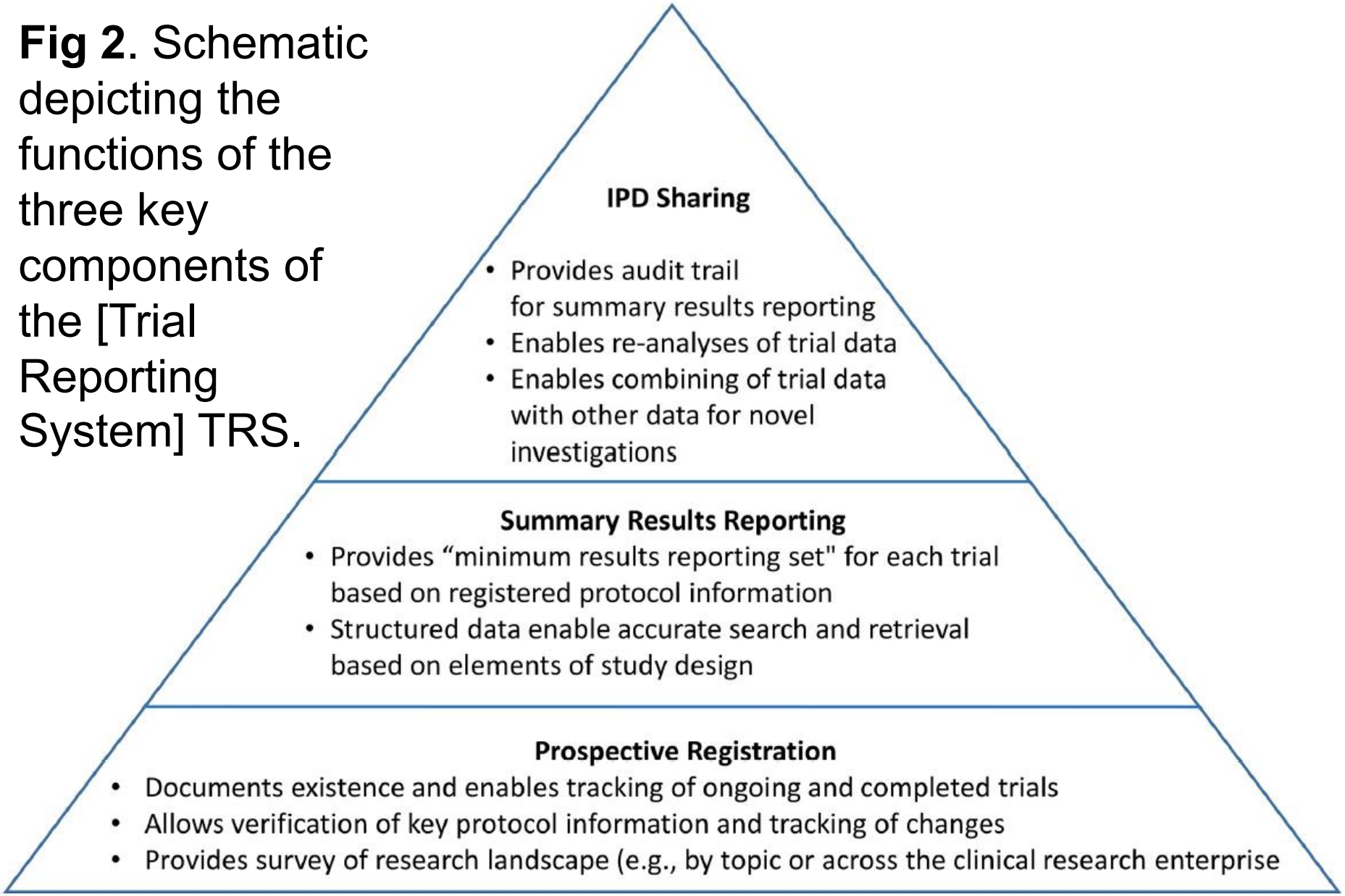
- “Every week, we will publish a brief piece describing one important unreported trial that could be used to improve patient care … Our initial sample of unreported trials will be drawn from those recently breaching the FDA Amendments Act of 2007 (FDAAA).”
- http://blogs.bmj.com/bmj/category/unreported-trial-of-the-week



http://fdaaa.trialstracker.net/

Comments on Individual Participant Data (IPD)

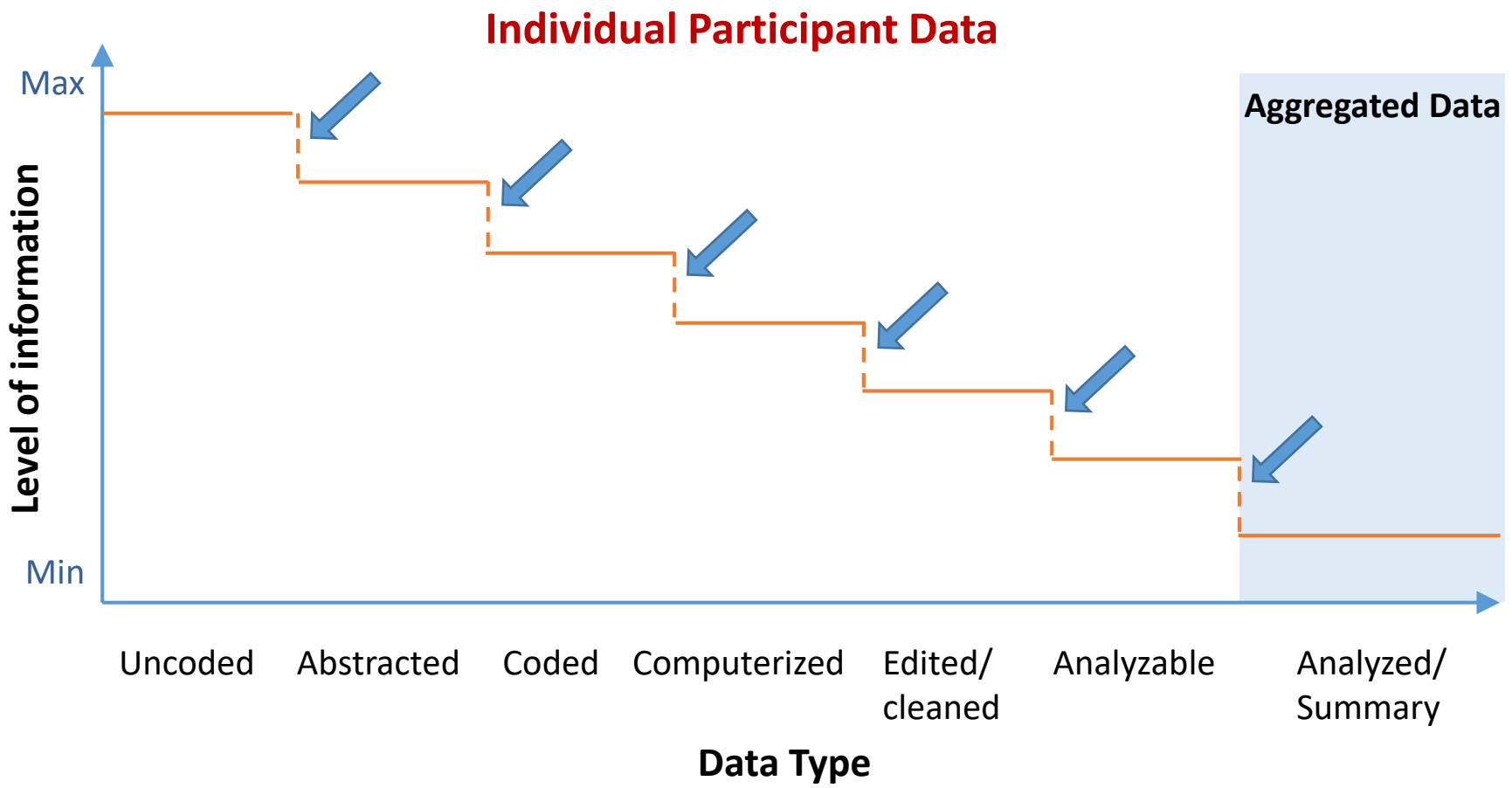
Fig 2. Schematic depicting the functions of the three key components of the [Trial Reporting System] TRS.



Zarin DA, Tse T. *PLoS Med*. 2016.

ClinicalTrials.gov

Journey from Uncoded Data to Summary Data



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

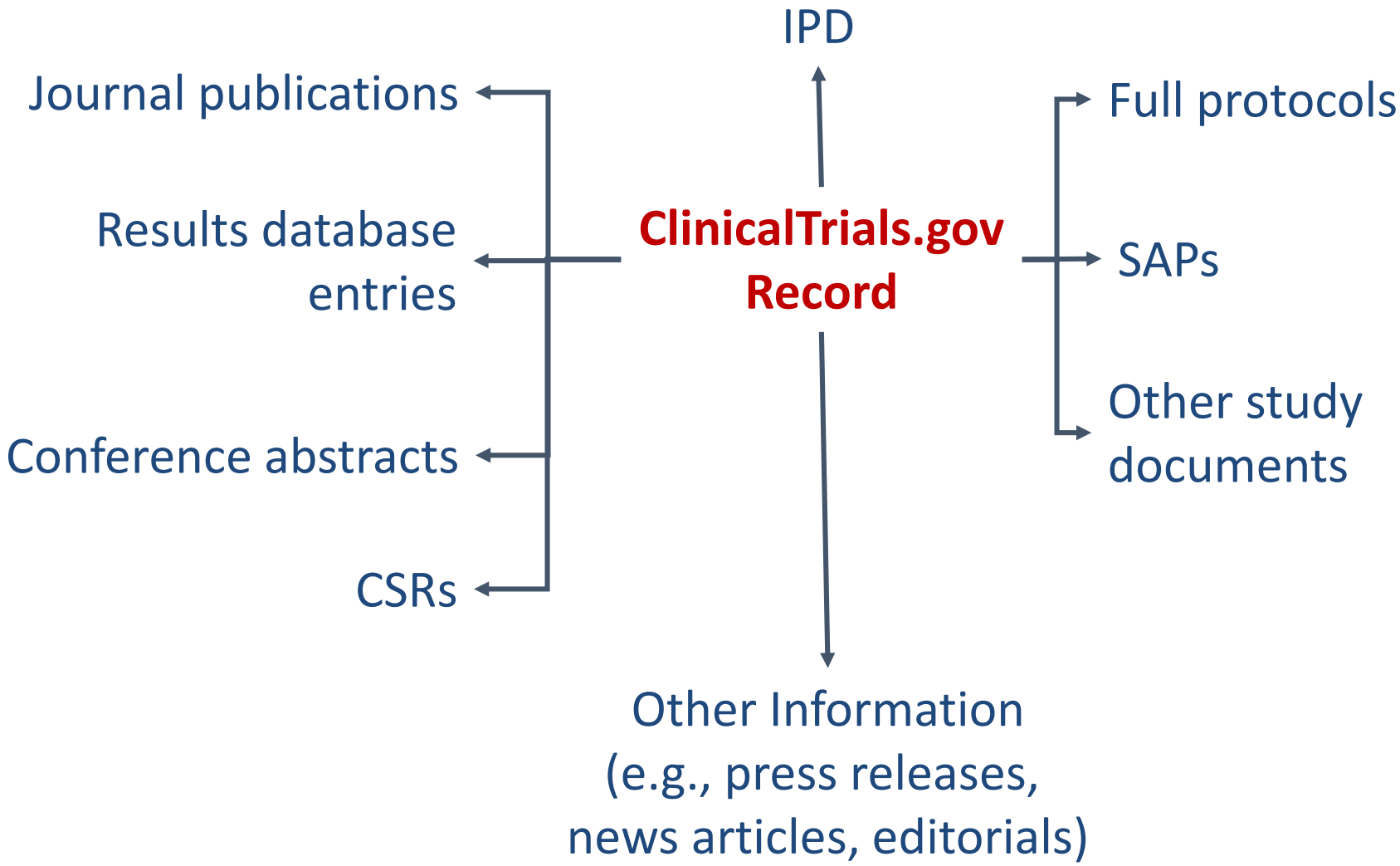
Plan to Share Individual Participant Data (IPD) Data Element

- **At Time of Registration** (Oversight module)
  - **Plan to Share Data?**
    - Definition: Indicate whether there is a plan to make individual participant data (IPD) collected in this study available. Select Yes/No/Undecided.
  - **Description**
    - Definition: If IPD collected in this study are to be made available, briefly describe what participant data are to be shared, when data will be available, and how the data may be obtained. An explanation may be provided for why IPD will not be shared.

Available Study Data/Documents Data Element

- **After Study Completed** (References Module)
  - **Available Study Data/Documents**
    - Definition: Study data sets and documents that are being shared. Provide the following information for each:
  - **Type**
    - Definition: The type of data set or document being shared.
      - Individual Participant Data Set
      - Study Protocol
      - Statistical Analysis Plan
      - Informed Consent Form
      - Clinical Study Report
      - Analytic Code
      - Other (specify)

ClinicalTrials.gov: Informational Scaffold



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

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.