Clinical Research Management Webinar Series

ClinicalTrials.gov:

Compliance for Academic Medical Centers and Research Sites

February 23, 2011

Experience. Redefined.®

A Bit About Our Speakers

Matthew Lester

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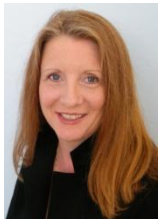
Matthew advises clients on research management issues with a focus on clinical research operations and compliance. His diverse experience includes projects related to federally funded laboratory-based research, industry sponsored clinical trials, strategic planning, and clinical trials billing compliance.



Barbara Godlew

President, FAIRE Company LLC
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Barbara is a recognized senior clinical trial disclosure expert and consultant for several major pharmaceutical companies. She has worked with numerous small, medium, and large pharmaceutical/biotechnology/medical device companies to assess and streamline their clinical trial disclosure operations, policies, and processes. Barbara is a founding member and current Chair of the Drug Information Association Clinical Trial Registry/Results Database Working Group, and has authored/co-authored numerous journal articles about clinical trial disclosure issues.

Agenda

- History - How did we get here?
- Key Drivers - Why is this important? What is driving the need for improved disclosure?
- Status - What is happening? Regulatory update
- Requirements - What are regulations?
- Compliance - How to prepare and how to avoid risks today?

Disclosure

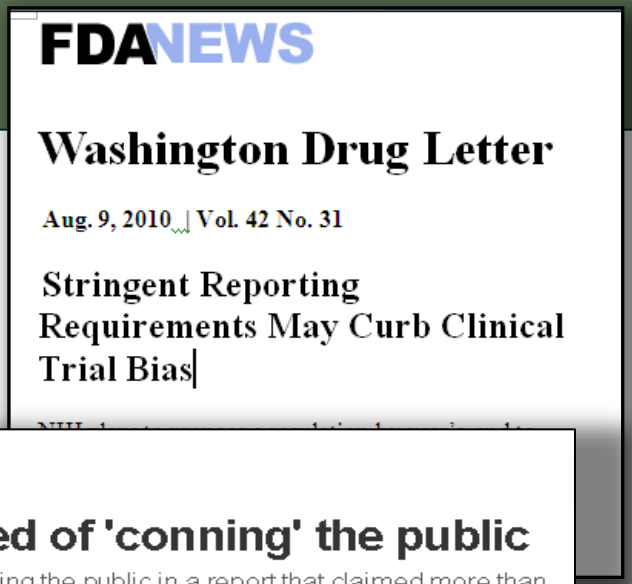
This presentation is intended to provide an overview of the evolution and current state of clinical trial registration and results disclosure. Regulatory requirements are paraphrased for clearer communication. However, the presentation should **NOT** be considered a complete or authoritative source of information. Consult your legal and regulatory representatives for additional clarification.

Clinical Trials Registration & Disclosure in the News

THE LANCET

Clinical trial registration: a statement from the International Committee of Medical Journal Editors

Altruism and trust lie at the heart of research on human subjects. Altruistic individuals volunteer for research because they trust that their participation will contribute to improved health for others and that researchers will

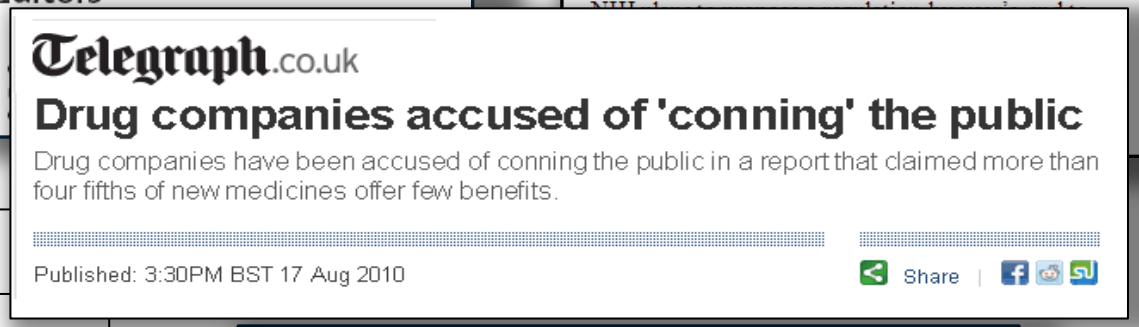


FDANEWS

Washington Drug Letter

Aug. 9, 2010 | Vol. 42 No. 31

Stringent Reporting Requirements May Curb Clinical Trial Bias



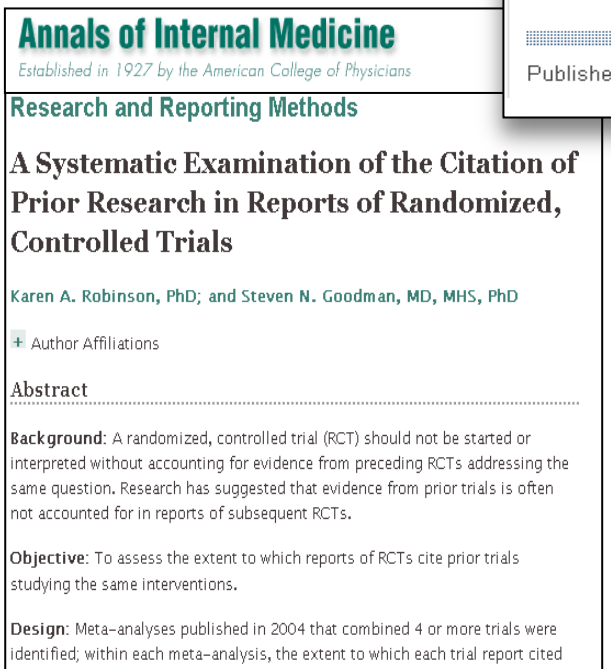
Telegraph.co.uk

Drug companies accused of 'conning' the public

Drug companies have been accused of conning the public in a report that claimed more than four fifths of new medicines offer few benefits.

Published: 3:30PM BST 17 Aug 2010

Share



Annals of Internal Medicine

Established in 1927 by the American College of Physicians

Research and Reporting Methods

A Systematic Examination of the Citation of Prior Research in Reports of Randomized, Controlled Trials

Karen A. Robinson, PhD; and Steven N. Goodman, MD, MHS, PhD

+ Author Affiliations

Abstract

Background: A randomized, controlled trial (RCT) should not be started or interpreted without accounting for evidence from preceding RCTs addressing the same question. Research has suggested that evidence from prior trials is often not accounted for in reports of subsequent RCTs.

Objective: To assess the extent to which reports of RCTs cite prior trials studying the same interventions.

Design: Meta-analyses published in 2004 that combined 4 or more trials were identified; within each meta-analysis, the extent to which each trial report cited

boston.com

GLOBE EDITORIAL

The Boston Globe

Publish data on drug trials — even when it's not flattering

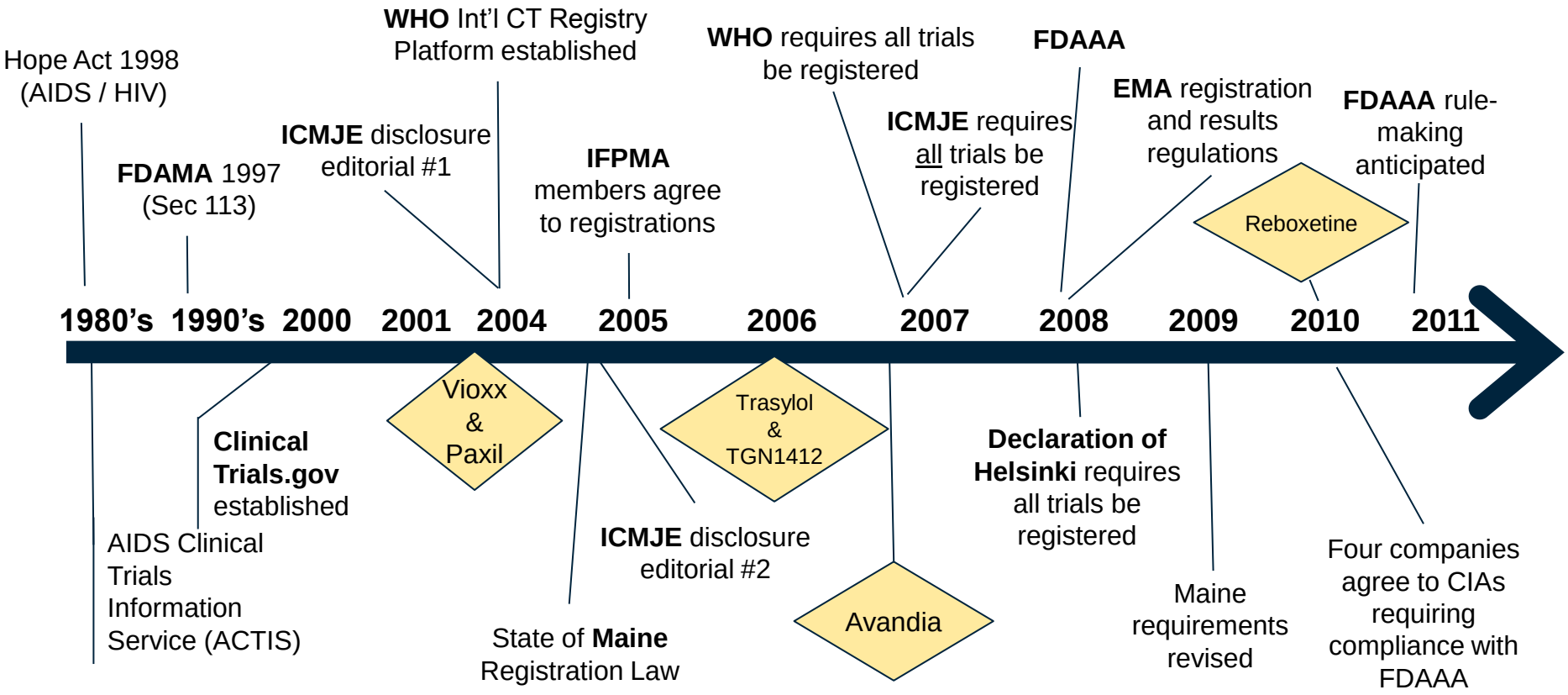
July 26, 2010

LURKING BENEATH some of the biggest prescription drug scandals of our time is the specter of unflattering data that was known to pharmaceutical companies and could have revealed problems sooner had it been made public. Now, an international federation of drug manufacturers, whose members include the industry's main players, has pledged to submit most clinical trial results for publication in peer-reviewed journals, whether the outcome is positive or negative.

This step should inject transparency into the now-murky process of data

Legislative Overview

Disclosure regulations started in the 80's, but only became critically apparent recently.



Registration is now mandatory in 15-18 countries* including:
Argentina, Canada, Croatia, Czech Republic, France, India, Israel, Italy, Hong Kong, South Africa, Taiwan, and the UK.

***Nothing in Antarctica…yet.**

Landscape Today

Cause

- Inconsistent reporting of protocols, results
- Unpublished data (reboxetine, paroxetine, rosiglitazone, rofecoxib)
- Lack of transparency of all stakeholders (industry, gov't agencies, journals)
- Need to reduce duplicate studies
- Non-compliance with previous regulations
- Regulations with no penalties
- Inconsistent reporting on organization-specific websites
- Call for additional safety information

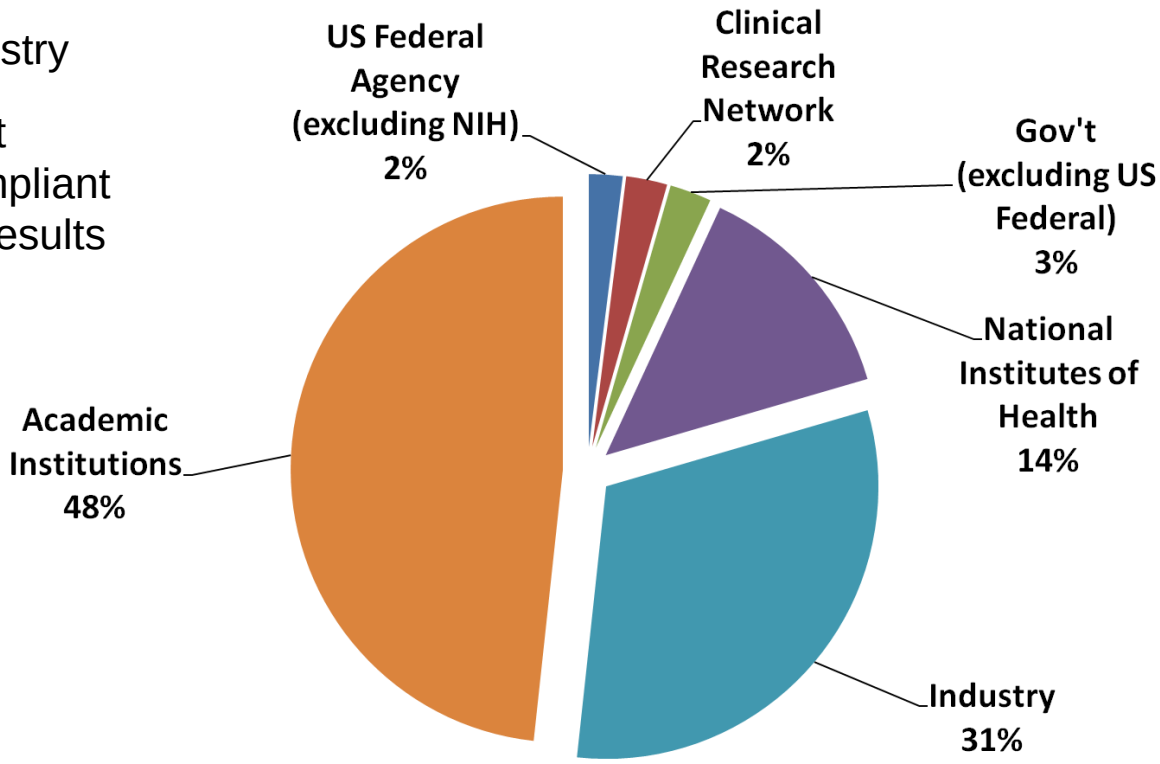
Effect

- Registration is a requirement for top-tier and many other medical journals
- FDAAA requires registrations and results reporting on ClinicalTrials.gov
- ClinicalTrials.gov as the 'de facto' standard
- High-profile legal action against large pharmaceutical companies
- Continued demand for more transparency in the drug development and clinical research process
- FDA can impose possible fines and penalties for non-compliance
- FDA, NIH and OIG are looking to enforce disclosure

Importance to Academic Institutions

- More *applicable* clinical trials are sponsored and conducted by academic medical centers, hospitals and independent research sites
  - 23,600 vs. 14,000 for industry
- NIH and FDA have found that academic institutions are compliant with FDAAA for posting trial results less than 5% of the time.
- Continued trust by the public and Congress is critical.
- Non-compliance can result in limits on or revocation of federally-funded research dollars

Total ClinicalTrials.gov Registrations by Type of Organization



Analysis of Clinicaltrials.gov data as of December 2010

Federal Government's Response….

"That's our new mission statement."

Enforcement Activity

- Currently, four pharma companies have corporate integrity agreements (CIAs) that also require FDAAA compliance.
- Per the CIA of one Company:
  - *"Within 120 days after the Effective Date, [Company] shall register all clinical studies and report results of such clinical studies on the National Institutes of Health (NIH) sponsored website (www.clinicaltrials.gov) in compliance with all current federal requirements."*
  - *"[Company] shall continue to comply with Federal health care program requirements, or other applicable requirements relating to the registration and results reporting of clinical studies throughout the term of this CIA."*
  - *"In addition, if there is a change in Federal health care program requirements, FDA requirements, NIH requirements, or other applicable requirements relating to registration and results reporting of clinical study information, [Company] shall fully comply with such requirements."*

NIH Sends Notices for 21,000 Studies

- In August 2010, the NIH sent notices to the responsible parties of approximately 21,000 (9,000 industry and 12,000 non-industry) trials that appeared to be missing data or lacking results in ClinicalTrials.gov.
- 30% were corrected or addressed
  - FDA regards the lack of response to the notice as “alarming.”
- Questions were raised by recipients as to the:
  - Intent of the notices
  - Data used for the analysis
  - Methods used to determine missing data

Informed Consent Changes

- On January 4, 2011, FDA amended the informed consent language requirements
- The following statement must be included in the informed consent document:

  "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

- Compliance required on March 7, 2012 for all trials initiated on or after the March 7, 2011.

- Potential increased FDA enforcement once these requirements go into effect

Source: 21 CFR Part 50.25(c)

FDAMA→ FDAAA

- Food and Drug Administration Modernization Act (FDAMA)
  - 1997 protocol legislation for all trials of serious and life-threatening conditions/diseases
  - No enforcement strategy → noncompliance
  - Does not address results reporting
- Food and Drug Administration Amendments Act (FDAAA)
  - 2007 legislation for all Phase II-IV interventional drug/device trials of products marketed in US*
  - Includes new indications for marketed products
  - Applicable to publicly AND privately-funded trials
  - Penalties for noncompliance:
    - $10,000 per grievance and potentially $10,000/day
    - Potential loss of current and future federal funding
  - Does not replace FDAMA
- FDA / NIH Rulemaking
  - Draft rules expected later this year
  - Lack of final rules
    - Creates confusion among data providers
    - Gives impression of “disclosure not necessary until final rulemaking”
    - Creates uncertainty of future requirements and resource needs

*Subject to interpretation pending final rulemaking. Refer to FDAAA for specific caveats

FDAAA Applicable Clinical Trials*

WARNING: Complicated definition generalized

- Phase II-IV controlled clinical investigations of FDA-regulated *marketed* drugs/biologics/devices or *new indications* of marketed drugs/biologics/devices
  - Includes IND Exempt studies
- Investigational new drug (IND) applications
- Investigational device exemption (IDE) applications
- Pediatric post-marketing surveillance device trials
- Does not include over-the-counter products
- May include trials with investigative sites outside of the United States

***More information available at http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf**

FDAAA Basics: Milestones

- **Registration**
  - Trials in serious, life-threatening conditions
    - Ongoing trials: 27 Dec 2007
    - New trials: within 21 days of FPFV
  - All other applicable trials
    - Ongoing trials: 27 Sept 2008
    - New trials: within 21 days of FPFV
- **Results**
  - Basic results: 27 Sept 2008
    - Demographic, baseline characteristics
    - Primary, secondary outcomes
    - Point of scientific contact
    - Investigators ability to discuss results
  - Serious/frequent adverse event:

    27 Sept 2009
  - Expanded results rules: 2011? 2012??
    - Lay and technical summary of results?
    - Posting trials of unapproved drugs?
    - Statistical analysis plan?
    - Full protocol?
    - Patient level data?

Registration vs. Results Reporting

Protocol

Results Reporting

FDAAA Protocol Registry

Minimum Dataset: 43 fields

- Unique Protocol ID
- Brief Title
- Official title
- Secondary IDs
- Study type
- FDA-reg intervention?
- IND/IDE protocol?
- IND/IDE grantor
- IND/IDE #
- IND/IDE serial #
- Section 801 trial?
- Delayed posting?
- Has expanded access?
- Sponsor
- Collaborators
- IRB approval?
- Approval status
- Approval number
- Board name
- Board affiliation
- Board contact info
- DMC?
- Oversight authorities
- Brief summary
- Overall recruit status
- Primary purpose
- Study phase
- Intervention model
- Study start date
- Primary completion date*
- Study completion date*
- Number of arms
- Arms descriptions
- Masking
- Conditions studied
- Eligibility criteria
- Gender
- Age limits
- Accepts healthy subjects?
- Central contact
- Study officials
- Investigators
- Investigator contact info

***Definition of study completion date changed with FDAAA enactment**

FDAAA Results Posting

Minimum Dataset: 59 fields
43 registration fields + 59 = 102 results reporting fields

- Results point of contact
- Certain agreements
- Participant flow
- Recruitment details
- Pre-assignment details
- Baseline characteristics
- Outcome measures
- Number of subjects analyzed
- Analysis population description
- Statistical analysis details
- AEs listings
- Total # affected by any SAE
- Total # affected by any AE
- Frequency threshold for AEs
- # Affected by specific AE
- # of AE events
- # participants at risk

*Additional data fields available if desired…

Example Results Record

- ClinicalTrials.gov currently requires separate outcome measures for individual time points

  Example: Blood glucose measure every 15 minutes x 4 hours = 16 outcome measures

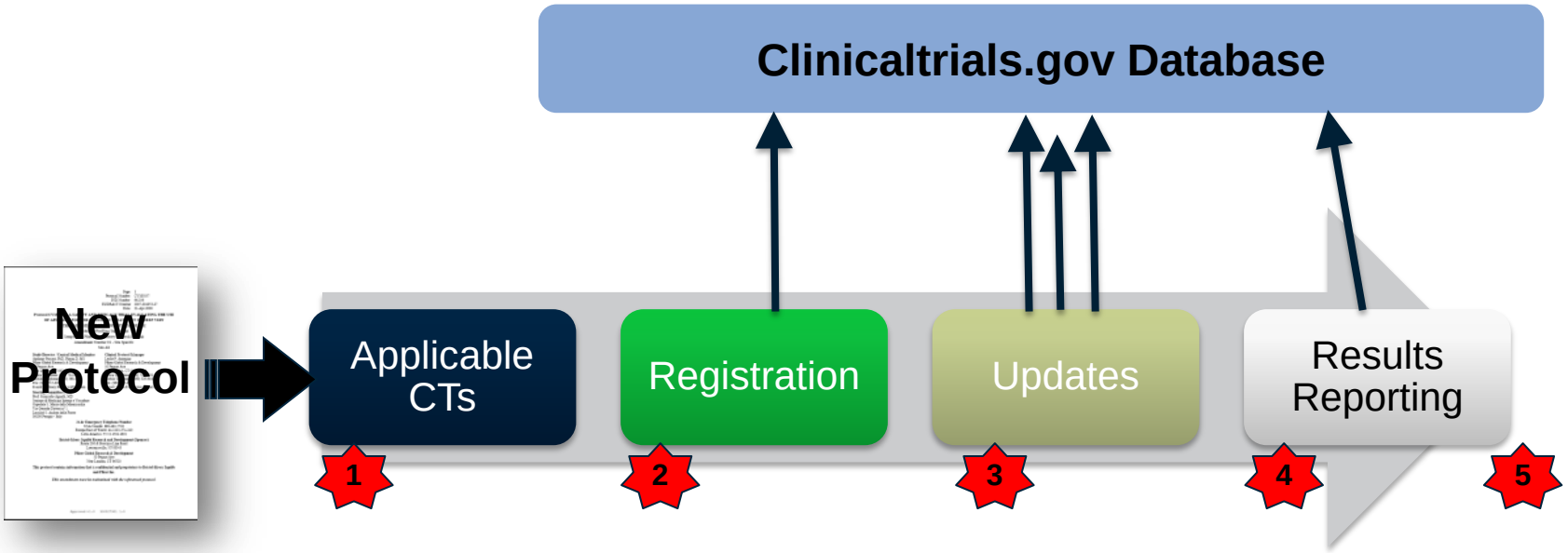
- Study of Multiple Doses of Saxagliptin (BMS-477118)
  http://www.clinicaltrials.gov/ct2/show/NCT00950599?term=BMS&rslt=With&lup_s=01%2F01%2F2010&lup_e=04%2F30%2F2010&rank=3

84 outcome measures!

- NIH estimates 20 hours per results record
  - 10 hours for initial submission plus two updates at 5 hours each
- Actual experience is 60 hours based on a survey of 52 pharma and biotech companies[1]
  - 22 hours gathering information
  - 17 hours for initial submission
  - 21 hours for revisions
- *The total hours depends on complexity of the trial*

1- McCarthy and Godlew, "ClinicalTrials.gov: A Questionnaire of Industry Experiences and Perceptions." Drug Information Journal, Vol. 44, pp. 233–241, 2010.

Compliance Risk Areas



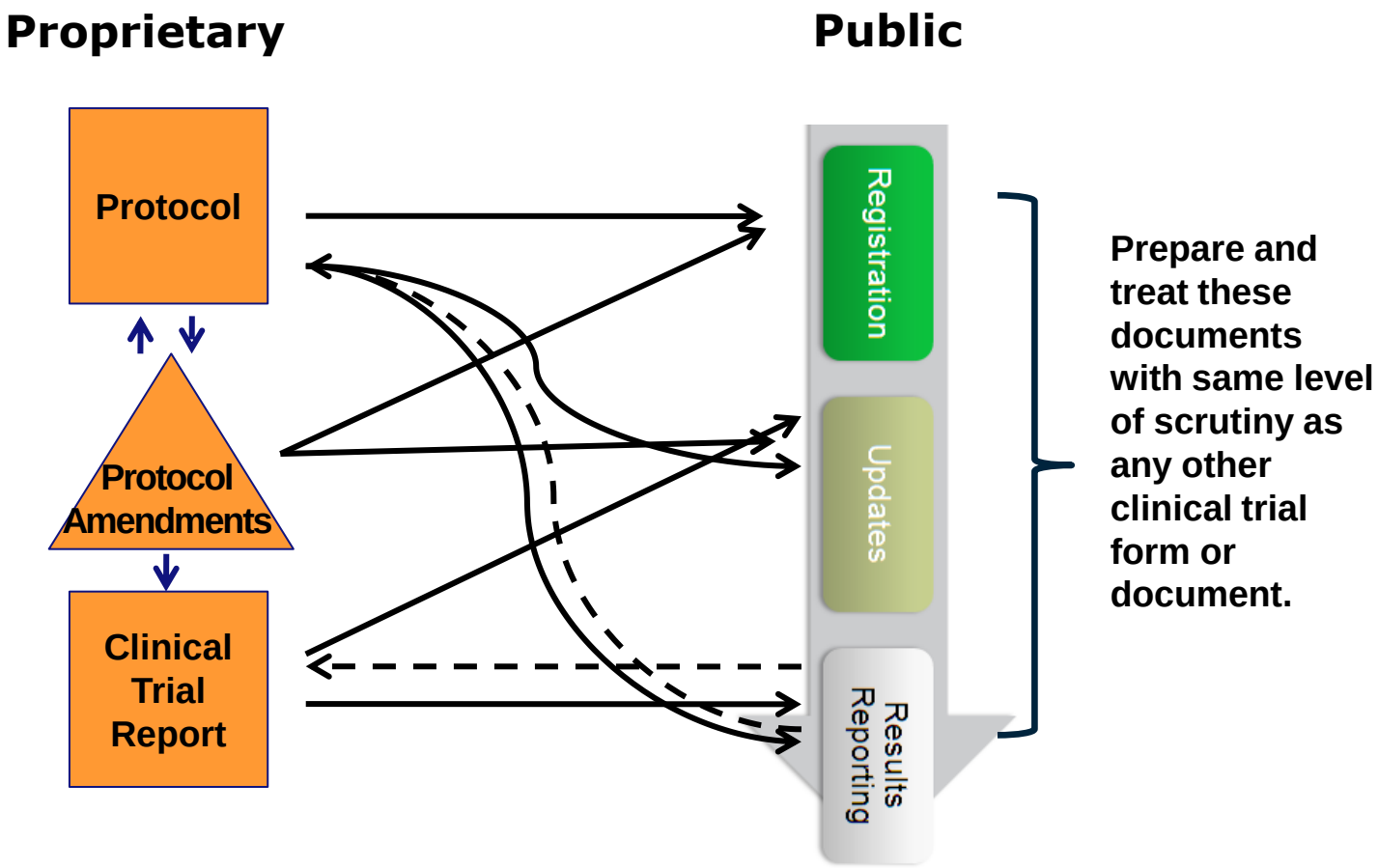
Key Risk Areas

1. Defining and identifying applicable clinical trials consistent with FDAAA, FDAMA, Maine, and European Medicines Agency (EMA)
2. Timely registration based on 1st patient enrolled
3. Updates on a periodic basis and changes in the study
4. Timely results reporting (12 mos. after final data collection for primary end point)
5. Publications and presentations are consistent with results posting

Important Considerations

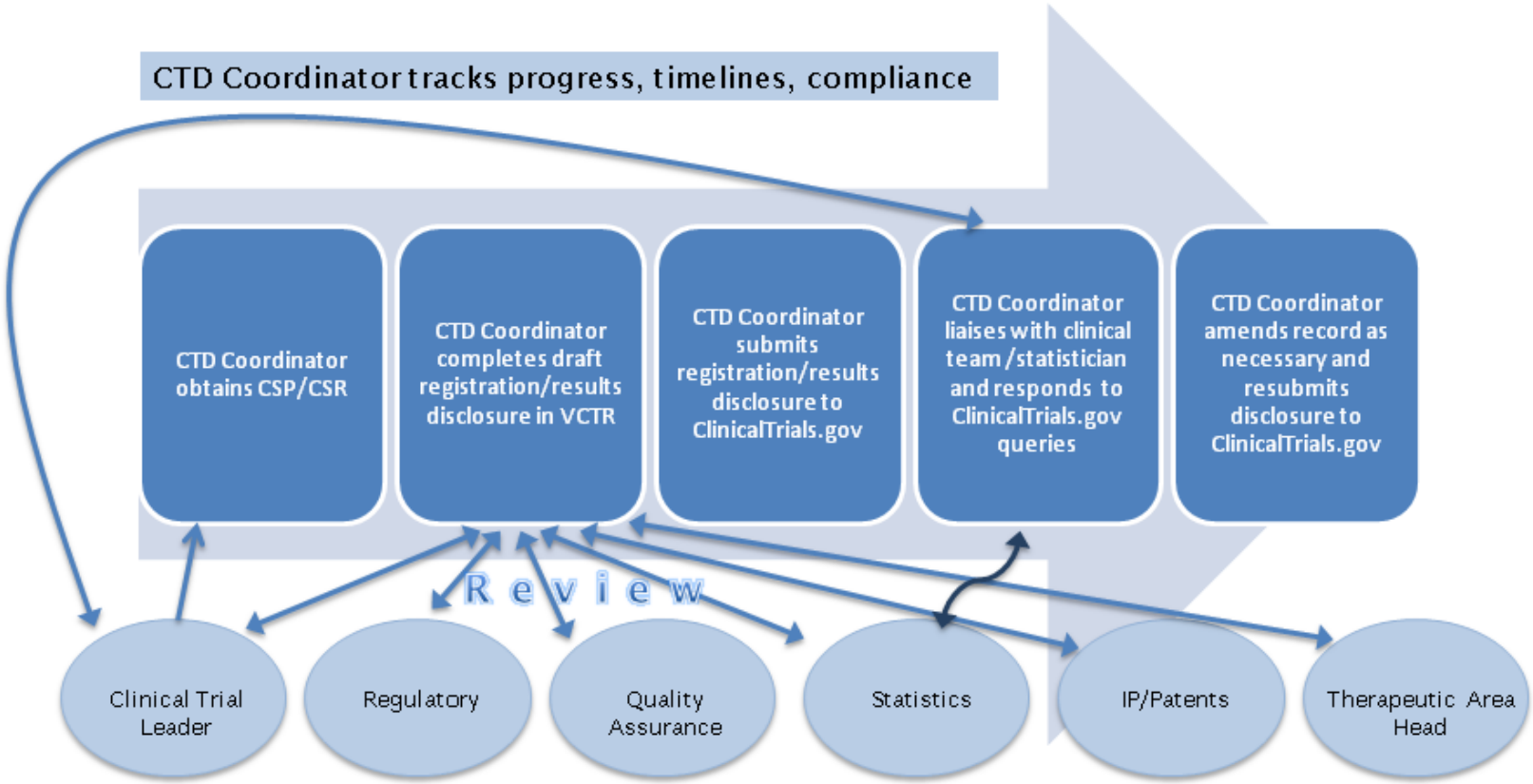
- What is your institution's policy on clinical trial disclosure?
- How does your institution define "observational?"
- How does your institution handle post hoc analysis reporting?
- Who does the 'leg work' to identify all manuscripts published by any investigator for a particular trial?
- Complicated protocols = intensely complicated results reporting
- Do you have adequate explanation for outcome measures? (scientifically appropriate tests, time points, etc.)
- How is the data expressed (rate, percentage, incidence, etc.)
- Do your adverse event summary tables match the unique formatting for ClinicalTrials.gov?
- Can the statistical analysis plan be "deciphered" without a statistician?
- How are multi-sponsor collaborative studies reported? Who owns the data?

Recognize the Complexity of Interrelationships



Operational Models

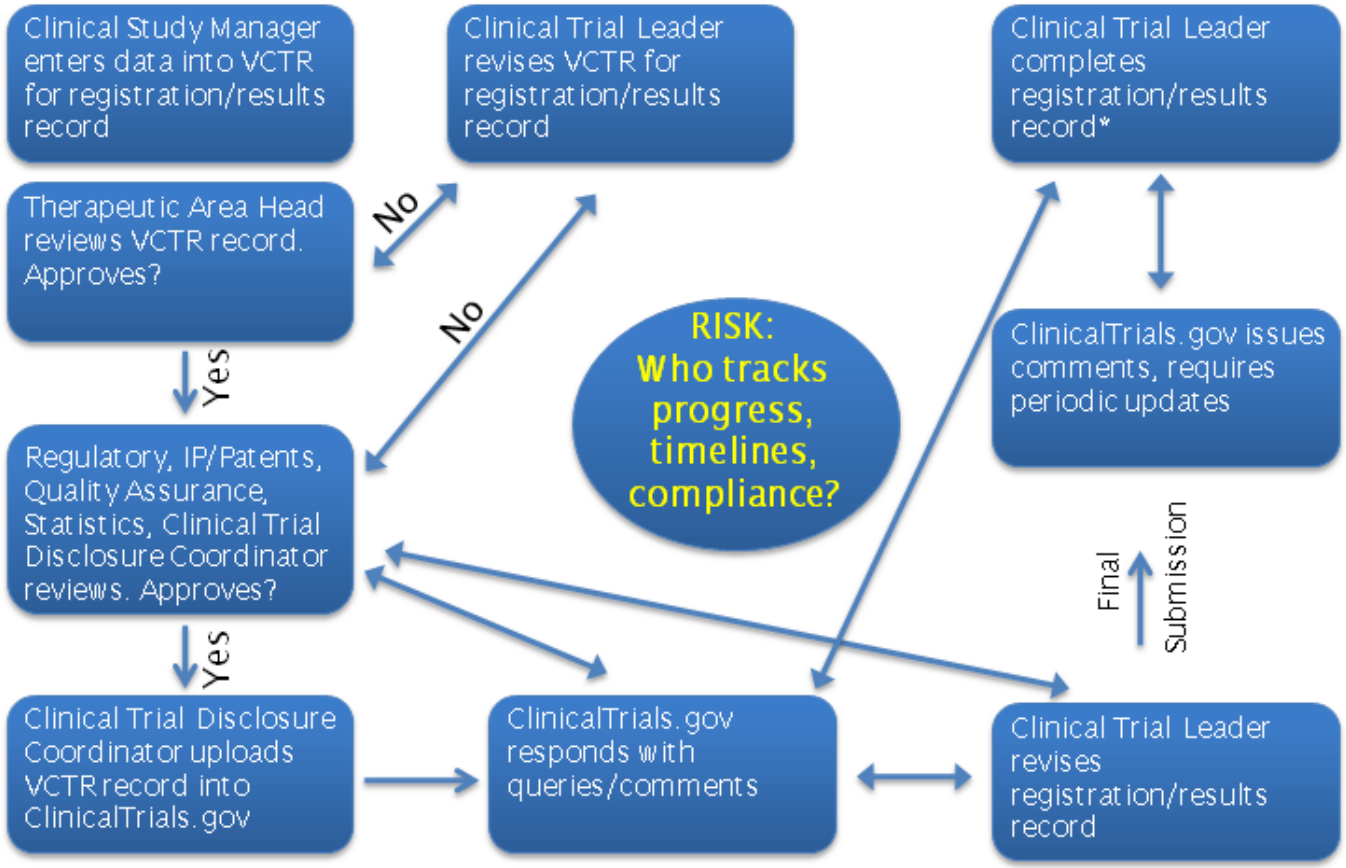
Centralized Example



Multiple review cycles may occur depending upon ClinicalTrials.gov reviewers.

Operational Models

Decentralized Example

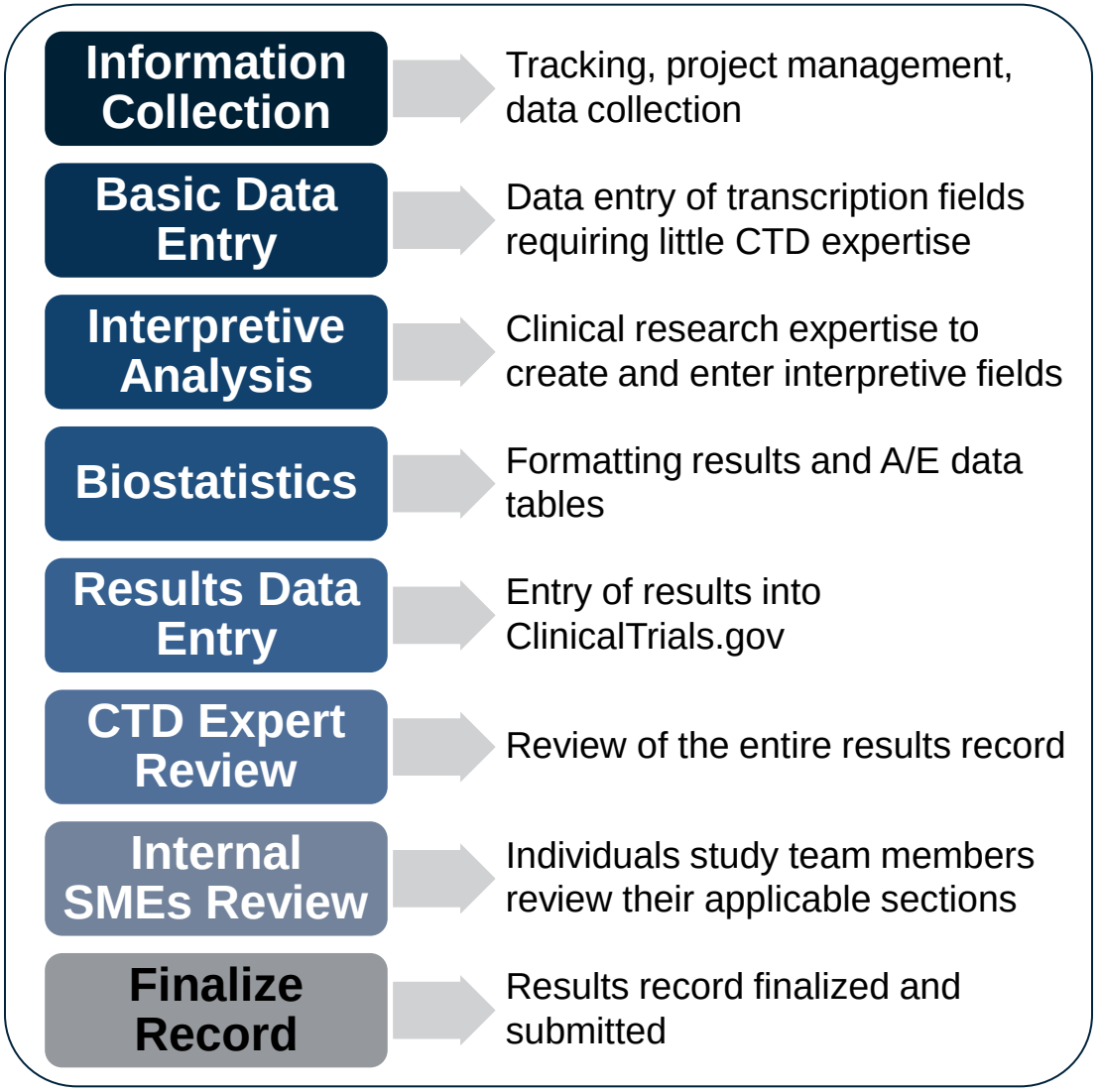


*Multiple review cycles may occur depending upon ClinicalTrials.gov reviewers.

Operational Models

Division of Labor Approach

- Correlate expertise and labor cost
- Allows for development of specialists



Industry Efforts to Achieve Compliance

- Establishing clinical trials disclosure office
  - Dedicated resources for disclosures
- Purchasing or developing software tools
- Outsourcing disclosure activities
- Develop matrix management across the organization (statistics, clinical trials, legal, QC, regulatory, etc) relevant for disclosure
- Industry meetings (e.g., DIA)
- Developing relationships with ClinicalTrials.gov staff at NIH

Preparing Now

- Don’t wait for final rulemaking
- Become familiar with your institution’s clinical trial disclosure policy.
  - Assess the applicability of other clinical trials disclosure requirements, including State of Maine, EMA, WHO, ICMJE, etc., and determine compliance.
- Assess your organization’s compliance with FDAAA clinical trials disclosure requirements at a minimum.
- Ensure that entries in ClinicalTrials.gov are consistent with internal records; address gaps in reporting.
- Confirm that current processes identify, track and post results within the 12-month deadline for applicable clinical trials.
- Reassess audit and monitoring processes for results posting.

Information Resources

Information Resources

- DIA Clinical Trial Registry/Results Database Working Group
  - Meets ~1st Tuesday every month
  - Contact Barbara Godlew (barbara.godlew@fairellc.com)
- NIH/ClinicalTrials.gov staff (register@clinicaltrials.gov)
- PRS Test Database (https://prstest.nlm.nih.gov/)…practice, practice, practice!!!
- Definitions, guides, helpful hints, presentations (http://prsinfo.clinicaltrials.gov/fdaaa.html)

- Protocol related
  - Protocol data element definitions: http://prsinfo.clinicaltrials.gov/definitions.html
  - Protocol detailed review items: http://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf
- Results related
  - Basic results data element definitions http://prsinfo.clinicaltrials.gov/results_definitions.html
  - Adverse event reporting: http://prsinfo.clinicaltrials.gov/AdverseEvents.html
  - NIH's pre-submission checklist: http://prsinfo.clinicaltrials.gov/pre-submission-checklist.pdf
  - Detailed review items: http://prsinfo.clinicaltrials.gov/ResultsDetailedReviewItems.pdf

Thank you for your participation

For further information, please contact:

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