CLINICAL TRIAL DISCLOSURE AND THE RISK OF NONCOMPLIANCE
JUNE 4, 2012

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President

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NOTE

This information is intended to provide an overview of the current state of clinical trial registration and results disclosure. Regulatory requirements are paraphrased for clearer communication. Sponsors should consult their Legal, Regulatory Affairs, and/or Clinical Trials Office departments for institutional practice and policy.

My Background

Background
- Current Chair of the Drug Information Association’s Clinical Trial Disclosure Special Interest Area Community
- 17 years in domestic/international clinical trial disclosure policies, processes, regulations, and medical writing
- 12 years of clinical/surgical experience
- Industry: led development of the operations group for clinical trial disclosure at Novartis Pharmaceuticals Corporation
- Peer-reviewed publications

Education and certification
- BA, Colorado State University
- Diploma in Nursing, Mennonite Hospital School of Nursing
- Medical Writing Certificate, Graham School, Univ. of Chicago
Agenda

- Current and historical background of clinical trial disclosure
- Stakeholders
- Disclosure legislative and stakeholder requirements
- Grant applications/progress reports
- Implications of noncompliance
- Challenges to using ClinicalTrials.gov protocol registration/results reporting system
- Informed consent changes
- How to find help

Pop Quiz

- How many have heard of ClinicalTrials.gov?
- How many have visited the ClinicalTrials.gov website?
- How many have prepared a protocol registration or assisted with a registration?
- How many have worked on a results posting?
- How many of you have ever seen a results posting?
Evolution of Disclosures

1855

These Pills are confidently recommended for all kinds of 
Hemorrh and Bilious diseases, Sour Stomach, Headache, 
Dizziness, Heartburn, Flatulence, and all Impurities of 
the Blood; one of the best medicines in the world for Piles, 
also highly useful in Rheumatism. 

If your liver is torpid and inactive, and you are troubled 
with Jaundice, then take these Pills, and be cured. 

Ladies in the turn of life will find these Pills a great 
help. 

Young ladies just budding into womanhood, above all 
others, need these Pills, to help through this critical period. 

Mothers should see to this! 

Children, crying their little lives away while worms eat up 
their vitals, may be cured, and their tormentors killed 
and driven away, by the timely use of this great medicine. 

We do not pretend to place this medicine before the pub 
lic as a perfect “cure-all” for every disease, because that 
is out of the question; we only wish to let you know JUST 
WHAT IT WILL DO, and so warn; and in this crowd, 
or once-half is told — for full particulars, see directions 
accompanied each box.
History of the World As I Know It

ClinicalTrials.gov

ClinicalTrials.gov currently has >125,000 trial registrations with locations in 179 countries

ClinicalTrials.gov is the vehicle for compliance to FDAAA Section 801 and the ICJME mandate⁎.

Additional registers may be used to comply with ICMJE.
Purpose of Clinical Trial Disclosure

- **Original**
  - Assist people gaining access to clinical trials
  - Assure participants in clinical trials that their contribution will be available to inform health care decisions

- **Evolutionary**
  - Verify protocol objectives match results in manuscripts
  - Verify that data are publicly available in a timely fashion after study end

Present Day — BMJ 2012

- Food and Drug Administration Amendments Act (FDAAA) Section 801 was enacted in 2007 and many institutions have not fulfilled their results disclosure commitments
- Most do a good job of posting protocols, but fail to monitor when results are due.

Studies completed between 1 January and 31 December 2009
High Profile Problem

- Completed trials with completion date in 2009 (n=5,642)
- FDAAA-mandated trials of approved products (n=738)\(^1\)\(^2\)
- Results reported (n=163)
- Results not reported (n=575)

<table>
<thead>
<tr>
<th>Entity</th>
<th>FDAAA trials with results</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>126</td>
<td>317</td>
<td>40</td>
</tr>
<tr>
<td>Mixed</td>
<td>25</td>
<td>265</td>
<td>9</td>
</tr>
<tr>
<td>NIH/government</td>
<td>4</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>108</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>163</strong></td>
<td><strong>738</strong></td>
<td><strong>22</strong></td>
</tr>
</tbody>
</table>

\(^1\)www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
\(^2\) included Phase II-IV trials of drugs, devices, biologics


STAKEHOLDERS
Trial Disclosure Stakeholders

- Sponsorship
- Protocol Development Coordinator
- Drug Safety
- Communications & Public Affairs
- Regulatory
- Scientific Communications
- Drug Safety
- Protocol Development Coordinator
- Clinical Investigator/Scientist
- Study Team Members
- Deans/Chair/Director of Research
- Institutional Review Boards
- Research Manager
- Grants & Contracts
- Information Technology
- Statistics and data managers
- Information Technology
- Legal

Stakeholders Interests

- Varies depending upon function
- Regulatory authorities and journal editors
  - Correct representation and disclosure of data
- Deans/dept heads/directors/IRBs
  - Proper disclosure, publication potential, grant funding
- Regulatory affairs/compliance
  - Compliance with law, institutional policy
- Investigators/study teams/statisticians
  - Process/operational issues, publication potential, data identification and integrity
FDAMA Section 113
Food and Drug Administration Modernization Act (1997)

Guidance for Industry
Information Program on
Clinical Trials for Serious or
Life-Threatening Diseases and
Conditions

- Affects Investigational New Drug (IND) applications of efficacy trials in serious or life-threatening diseases/conditions
- FDA considers all Phase II-IV trials with efficacy endpoints as trials to test effectiveness
- Phase I trials with efficacy endpoints may qualify
FDAAA Section 801
Food and Drug Administration Amendments Act (2007)

- Applicable clinical trials (ACTs) of compounds approved for marketing in the US (FDA-approved)
- Trial protocols must be registered within 21 days of study start
- Trial results must be reported within 1 year of primary completion date (in most cases)
  - Delayed disclosure of results possible for unapproved products or new indications
  - Results for unapproved products and new indications due 30 days after receipt of complete response letter from FDA

FDAAA Section 801—Protocols

**WARNING: Complex definition simplified!**

- **Protocol registration—ACTs**
  - Phase II, III, IV interventional trials in marketed products or for new use/indication in drugs, biologics, or devices subject to FDA regulation with 1+ sites in the US
  - Conducted under IND or investigational device exemption (IDE)
    - Can be an ACT even if not under IND (e.g., Phase IV investigator-initiated trial not looking at new use/indication)
  - Compound manufactured in the US (or its territories)
  - Conducted outside US, but within FDA jurisdiction

- Trials that **DO NOT** require FDAAA registration
  - Phase I trials (may need to register to meet FDAMA)
  - Observational studies

http://prsinfo.clinicaltrials.gov/fdaaa.html. Subject to change based upon rulemaking
Protocol Registration Timelines

Review criteria to determine if applicable clinical trial (ACT) needs to be registered on ClinicalTrials.gov per FDAAA:

- If the ACT was initiated after 9/27/2007...
- If the ACT was initiated on or before 9/27/2007 and was ongoing as of 12/26/2007 and involved a serious or life-threatening disease or condition...
- If the ACT was ongoing as of 9/27/2007 and involved a serious or life-threatening disease or condition and primary completion date occurred by 12/26/2007...
- If the ACT was ongoing as of 9/27/2007 and DID NOT involve a serious or life-threatening disease or condition and primary completion date occurred by 12/26/2007...

This timeline may not address every situation. Appropriate research office, general counsel, or other similar officials should be involved in determining whether if a trial is an ACT and required to be registered under FDAAA.

FDAAA Section 801—Results

WARNING: Complex definition simplified!

- Results reporting—ACTs
  - Same trial types as protocol registration
  - Most results submissions to ClinicalTrials.gov due no later than 12 months after primary completion date
    - Primary completion date: Last visit of last patient specifically for purposes of data collection for primary outcome measure of the trial--NOT to be confused with “Last Patient Last Visit”
  - Trials that DO NOT require FDAAA results reporting
    - Phase I trials
    - Observational studies

Results Reporting Timelines

Review the following criteria to determine if the applicable clinical trial (ACT) needs results posted to ClinicalTrials.gov per FDAAA:

- If the ACT was completed prior to 9/27/2007...
- If the ACT was initiated on or after 9/27/2007 and primary completion date occurred after 12/30/2007 and involved a serious or life-threatening disease or condition...
- If the ACT’s primary completion date and the completion date do not coincide (are not the same date)...
- If the ACT was initiated on or after 9/27/2007 and primary completion date occurred after 12/30/2007 and DID NOT involve a serious or life-threatening disease...
- If the ACT was ongoing as of 5/27/2007 and involved a serious or life-threatening disease or condition and primary completion date occurred before 12/30/2007...
- If the ACT was ongoing as of 5/27/2007 and DID NOT involve a serious or life-threatening disease or condition and achieved primary completion before 12/30/2007...

This timeline may not address every situation. Appropriate research office, general counsel, or other similar officials should be involved in determining whether if a trial is an ACT and required to be registered under FDAAA.

ICMJE
INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS

- Policy announced and evolved since 2004
- Requires protocol registration of all interventional clinical trials prior to study start
  - Any trial prospectively assigning health-related interventions to evaluate effects on health outcome
    - Intervention: drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care change
    - Health outcomes: biomedical or health-related measures including pharmacokinetic measures and adverse events
  - Noncompliance will likely result in nonpublication
- Observational trials* do not require registration

*assignment of medical intervention is not at discretion of investigator
Potential for More Elements in FDAAA

- Expansion of results requirement is being considered during final rulemaking process
  - Expansion of ACT definition?
  - Summary of trial and results in lay language?
  - Technical summary?
  - Full protocol?
  - Unapproved products?
  - Other categories as the HHS Secretary determines appropriate?
- Draft rules—no well-defined projected timeline
Grant Applications

- For competing applications that include ACTs:
  - Human Subjects Section of the research plan must include
    - Clear statement, under a heading entitled “ClinicalTrials.gov”, that project includes an ACT requiring registration in ClinicalTrials.gov
    - Identity of responsible party + contact information
    - NCT number
    - Brief Title as defined by ClinicalTrials.gov
  - The Authorized Organizational Representative (Signing Official) signature assures compliance with FDAAA.

- Applies to all applications submitted to NIH on or after January 25, 2008 with an ACT in the proposed project
Grant Progress Reports

- Non-competing progress report that includes ACTs
  - Human Subjects Section of the research plan must include
    - Responsible party + contact information
    - NCT number
    - Brief Title as defined by ClinicalTrials.gov
  - The signature on the non-competing continuation progress report of the Authorized Organizational Representative (Signing Official) assures compliance with FDAAA
- Applies to all progress reports for grants with ACTs with budget start dates of April 1, 2008 or later

Who Registers the Trial and is the Responsible Party?

- The Sponsor
  - Company/organization initiates the trial and its employees conduct the trial: it must register the trial
  - Multicenter trials: generally pharma/biotech/medical device company/organization
  - Can also be an individual who initiates a trial, but has someone else conduct the investigation
  - NIH/FDA considers holders of an IND or IDE the sponsor/responsible party (i.e., sponsor-investigator)
- The Principal Investigator
  - Investigator is responsible for conducting trial, controls data, and has rights to publish results: investigator must register the trial and is responsible party
NONCOMPLIANCE

What Could Possibly Go Wrong?
- Certification of compliance with FDAAA required by the NIH is different than that required by FDA
- FDA requires FORM 3674

### Certification Statement / Information

$ CHECK ONLY ONE OF THE FOLLOWING BOXES (See instructions for additional information and explanation)

A. I certify that the requirements of 42 U.S.C. § 282(j)(ii) of the Public Health Service Act, enacted by 21 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

B. I certify that the requirements of 42 U.S.C. § 282(j)(ii) of the Public Health Service Act, enacted by 21 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

C. I certify that the requirements of 42 U.S.C. § 282(j)(ii) of the Public Health Service Act, enacted by 21 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.


NCT Number(s):

The undersigned declares, to the best of his/her knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(ii)(B), section 4229A of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 361 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

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**Noncompliance with FDAAA**

- **FDAAA**
  - Criminal and/or civil penalties
  - $10,000 for first event; $10,000 per day for every day late (if not corrected within 30 days)
  - Public notice of failure in registry/results data bank
  - Corporate integrity agreements have disclosure sections
- **Grants/progress reports**
  - Withholding remaining or future grant funding or recovery of monies already allocated
  - NIH will verify each ACT for which the grantee is the responsible party has been registered in ClinicalTrials.gov
Noncompliance with ICMJE

- Not registering trial on ClinicalTrials.gov prior to study start **almost certainly disqualifies** manuscript from publication
- **BMJ rejects 10-20 manuscripts/year for failing to register a clinical trial prospectively** in line with ICMJE policy¹
- **As of Nov 2011, NEJM has rejected 66 papers for registration issues** (8 for lack of proper registration, 58 for late registration) and have not granted appeals²
- Many institutions have had manuscripts rejected for noncompliant protocol registration
- Many non-ICMJE journals follow ICMJE practices

¹Personal communication between Barbara Godlew and Pamela Miller, NEJM. 28 Nov 2011.
²Personal communication between Barbara Godlew and Trish Groves, BMJ. 28 Nov 2011.

According to an article in the upcoming issue of *The New England Journal of Medicine,* all your fears are well founded.
ClinicalTrials.gov—Protocol and Results System

https://register.clinicaltrials.gov/

Need Access to PRS?

http://prsinfo.clinicaltrials.gov/
## Protocol Registry Minimum Dataset: 43 fields

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

*Definition of completion date changed with FDAAA enactment

## Minimum Results Dataset: 59 fields*

**PLUS ALL 43 fields from NIH registry dataset**

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results point of contact</td>
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<tr>
<td>Certain agreements</td>
<td></td>
</tr>
<tr>
<td>Participant flow</td>
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<tr>
<td>Recruitment details</td>
<td></td>
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<tr>
<td>Pre-assignment details</td>
<td></td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
</tr>
<tr>
<td>Number of subjects analyzed</td>
<td></td>
</tr>
<tr>
<td>Analysis population description</td>
<td></td>
</tr>
<tr>
<td>Adverse events (AE) listings</td>
<td></td>
</tr>
<tr>
<td>Total # affected by any serious AE</td>
<td></td>
</tr>
<tr>
<td>Total # affected by any AE</td>
<td></td>
</tr>
<tr>
<td>Frequency threshold for AEs</td>
<td></td>
</tr>
<tr>
<td># Affected by specific AE</td>
<td></td>
</tr>
<tr>
<td># of AE events</td>
<td></td>
</tr>
<tr>
<td># participants at risk</td>
<td></td>
</tr>
</tbody>
</table>

*Additional data fields available if desired...
Challenges with Registering Protocols

- **Importance of a well-written protocol with well-written objectives/outcome measures cannot be understated**
- ClinicalTrials.gov generally allows 1 primary outcome measure
- No limit to secondary outcome measures
- Multiple outcome measures increase workload *exponentially*
- Multiple time points per outcome measure = multiple outcome measures
  - BP measured every 15 minutes for 4 hours = 16 outcome measures
  - EXAMPLE: NCT00048568 has **146** secondary outcome measures due to this requirement (took many weeks to enter data for this trial)

Challenges in Reporting Results

- Tool somewhat nonintuitive
- Data fields somewhat inflexible
- Lack of standardized review procedures*
- Identifying data and data sources
- Results for outcome measures with multiple time points
- Resources
  - Simple results record**: Gathering, entering, reviewing data for results record can take **20-30 hours** per trial depending on complexity
  - Rigorous internal reviews and QA required
- Multiple review cycles with ClinicalTrials.gov QA staff highly likely

*both with sponsors/institutions and and ClinicalTrials.gov review staff
**1 primary outcome measure, 2-3 secondary outcome measures
A Few Words About Adverse Events

- 2 adverse event tables
  - Serious adverse events (all)
  - All other adverse events
    - Excluding serious adverse events
    - Recommended frequency threshold is >5% in any arm
- Provide programmers with these specs to avoid future rework (these are nonstandard tables)
- Include standard source vocabulary such as MedDRA 10.0 or SNOMED CT

INFORMED CONSENTS
Informed Consent Changes (1)

- New rules effective 07 March 2012
- **Exact language** from FDA’s Compliance Program Guidance Manual **must be included** on informed consents for ACTs
  
  “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.”

- **Re-consent**, based solely on the new requirement, of trial participants **in trials that were initiated before the compliance date NOT required**, even if the consent needed to be amended for other reasons.

Federal Register / Vol. 76, No. 2 / Tuesday, January 4, 2011 / Rules and Regulations

Informed Consent Changes (2)

- Language must be included even when industry/NIH does not provide it in their templates
- If an IRB waives requirement for a signed written consent form, but requires investigators to provide subjects with a written statement regarding the research, FDA requires the new language be included
- If ACT is a multi-site trial and ICs have been cleared or approved for one or more sites, but not for all sites before the compliance date, the trial is considered to have initiated before the compliance date.

Federal Register / Vol. 76, No. 2 / Tuesday, January 4, 2011 / Rules and Regulations
Helpful Hints

- **Disclosure is an integral part of conducting clinical research**
- Identify all ACTs
- Determine if grant supports an ACT and who is responsible party
- Register ACT prior to study start, but no later than 21 days after enrolling the first subject and regularly update information in the record.
- Report ACT results not later than 1 year after the primary completion date
- Determine if ACT qualifies for delayed results reporting
- Determine how to handle 3rd party licensing agreements
- Include a certification of compliance (Form 3674) in grant application, progress report, IND, etc.
- Verify new informed consent letter for ACTs
Thoughts About Registering/Reporting

- Familiarity with clinical trial design, protocols, data, statistical methods
- Knowledge of a specific trial’s data or access to study manager and statistician
- Ability to make decisions consistent with institutional policy to interpret a (sometimes) ambiguous law
- Editorial attention to finer details of language and style
- Adaptability, flexibility in managing dynamic system with multiple players and priorities
- Patience, juggling skills, and a sense of humor
- Have a ‘Buy Your Statistician Lunch Day’

Key Questions (1)

- How do you track trials that need registering and when they need to have results reported?
- Do you have process maps and standard operating procedures for registration and results disclosure?
- Do your researchers know if they are the responsible party?
- Who files the grant applications and progress reports? Are they aware of FDAAA requirements to register/report?
- Have you developed forms to standardize the registration and results process?
Key Questions (2)

- Where does the protocol and results data exist inside your organization?
- Can you leverage systems to upload protocol information into ClinicalTrials.gov?
- Who identifies, reviews, and enters results data? Do you have your statisticians involved (HINT!)?
- Can you upload XML datasets for reporting results?
- Do you have a backlog of trials that need results reported?
- How do you get resource support for disclosure activities?

Coping With Disclosure Activities

Adapted from J M Fisher (©2003). Free use for personal and organizational development provided this notice is retained.
Where To Find Help

- Drug Information Association Clinical Trial Disclosure Special Interest Area Community (www.diahome.org)
  - >200 members
  - 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)

Thank You!

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