Presenting a live 90-minute webinar with interactive Q&A

Clinical Trials Disclosure and Reporting Compliance
Navigating Overlapping and Evolving Federal and State Transparency Requirements

THURSDAY, MARCH 31, 2011
1pm Eastern | 12pm Central | 11am Mountain | 10am Pacific

Today’s faculty features:

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Eve M. Brunts, Partner, Ropes & Gray, Boston

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Clinical Trials Disclosure and Reporting Compliance

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Clinical Trials Disclosure and Reporting Compliance

• Introduction: FDAAA
• Regulations and guidance related to clinical trial transparency
  – State laws on disclosure (trends, key differences among states, key areas of dispute)
  – Physician Payment Sunshine Act
  – Other transparency legislation
  – Conflict of interest legislation
• Corporate Integrity Agreements
• Foreign/international clinical trials
Predecessor to FDAAA: FDA Modernization Act, FDAMA

- Created the Clinical Trials Data Bank
- Mandated registration of all efficacy drug trials for “serious or life-threatening diseases and conditions” conducted under INDs
- To be posted, results were required to have already been published in a peer reviewed journal
“Responsible party" (sponsor or designated PI) to register and report results of "applicable clinical trials“
- Interventional studies of FDA-regulated products
- One or more sites in the U.S. (or territories)
- Product manufactured in the US or study conducted under an IND or IDE
- **Drugs and Biologics:**
  - Controlled clinical investigations other than Phase I
- **Devices:**
  - Controlled trials with health outcomes of FDA-regulated products (other than small feasibility studies) and pediatric postmarket surveillance studies
• **New** studies (other than Phase I) from 12/07: Register
• **Completed** studies from 12/08: report
• **Link** to registry entry and to any Medline cites to published results
• Applies to a wide array of research:
  – Any condition
  – Any sponsor type (industry, government, or academic)
• Expands on required fields, consistent with ICMJE, WHO
• **Devices** not previously cleared or approved: posted only after FDA approval/clearance
FDAAA: Elements for Registry of New Studies

- **Descriptive info** (title, design, primary/secondary outcome measures)
- **Recruitment info** (eligibility, recruitment status)
- **Location and contact information** (site-specific)
- **Administrative info** (protocol number, IND/IDE, ethics committee vote)
FDAAA: Elements for Results of Completed Studies

- **Demographic** and baseline characteristics
- Number of **dropouts**
- Primary and secondary **outcomes**
- Point of **contact**
- Certain **agreements** between sponsor and PI
  - E.g., restrictions on PI to discuss or publish results after study completion
FDAAA Deadlines and Dates

- 12/07: Register new studies; ongoing studies: update
  - New: register within 21 days after the first patient is enrolled
  - Updates: at least every 12 months
- Recruitment status: update within 30 days of any change
- Registration of trial results (publication irrelevant)
  - Within 1 year of earlier of either the estimated or actual date of last patient’s last visit specifically for data collection for primary trial outcome
  - Within 30 days of authorization for a new drug
    - Trial still ongoing with blinded data: extension may be possible
  - Adverse events data: must collect and report within 2 years
Enforcement measures for non-compliance with FDAAA § 801

- Loss of NIH grant support
- Fine: $10,000 for first event
  - $10,000 per day for every day late (if not corrected within 30 days)
  - No upper limit
- Named in the non-compliance list posted on ClinicalTrials.gov
Limitations on Disclosures Under FDAAA

• Submission not required:
  – Phase I data
  – Observational studies, such as post-approval safety monitoring
  – Older trials of drugs approved before 9/27/07, and that were no longer the subject of ongoing trials on or after 9/27/07
  – Results of trials of drugs that were never approved
    • Trials of previously approved drugs that have not been approved for a new indication will have to be posted, but not until 2 years after the completion date

• **Not addressed:** flawed design, choice of outcome, choice of comparator, ethical lapses, fraudulent data, misrepresentation
• FDCA bars FDA from disclosing “any method or process which is a trade secret entitled to protection”
• FOIA: Under exemption 4, agencies need not release “trade secrets and commercial or financial information [that is] privileged or confidential.”
• Redactions: may impair understanding
Clinical Trials Disclosure and Reporting Compliance: State Laws

Stafford Legal Webinar

March 31, 2011

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ROPES & GRAY LLP
Overview of State Laws

- One state (Maine) has specific law addressing disclosure of clinical trial information.
- Eight states currently have laws requiring disclosure of financial interactions with health care providers and/or compliance programs restricting such financial interactions:
  - States
    - California
    - District of Columbia
    - Maine
    - Massachusetts
    - Minnesota
    - Nevada
    - Vermont
    - West Virginia
  - Laws may address clinical trial payments.
Maine Clinical Trial Reporting Law

- Manufacturer or labeler of prescription drugs (or device delivering prescription drugs) must register a “covered clinical trial” on www.clinicaltrials.gov and subsequently post information concerning the results of the clinical trial

- Definition of “Covered Clinical Trial”
  - Manufacturer or labeler must sponsor or conduct “clinical trial” and clinical trial must involve FDA-approved drug that is or has been dispensed, administered, delivered or promoted in Maine
• Clinical Trial
  – Hypothesis-testing “clinical investigation” as defined by FDA
  – Post-marketing clinical study (includes observational studies)
  – Clinical study testing bioequivalency of drug against another drug
  – **Excludes** Phase I clinical trials
Maine Clinical Trial Reporting Law

Clinical Trial Registry Information (24 Elements)

- Trial identifying information (unique ID)
- Protocol title (lay public)
- Official scientific title
- Nature of investigation (interventional, observational)
- Name of funding organization(s)
- Name of sponsor(s)
- Description of protocol
- Date protocol information verified
- Recruitment status
- Dates of enrollment, implementation, final data collection
- Availability drug outside clinical trial
- Primary strategy subject identification (observational only)
- Primary outcome measure
- Secondary outcome measures
- Arms, groups and interventions
- Type of intervention
- Primary disease or condition
- Description of population from which groups selected (observational)
- Summary eligibility criteria
- Name and location of sites
- Contact information for sites (or central contact) plus principal investigator information
- Links or citations to articles on trial
- Links to websites on trial or drug product (includes FDA recall and safety alert links)
Maine Clinical Trial Reporting Law

• Clinical Trial Results Information
  – Submit results information to complete following fields on clinicaltrials.gov:
    • Results Point of Contact
    • Certain Agreements
    • Participant Flow
    • Baseline Characteristics
    • Outcome Measures
    • Adverse Events
  – Ongoing duty to update submissions with any post hoc analysis by or on behalf of manufacturer/labeler that includes an “objectively significant” correction or deviation
Maine Clinical Trial Reporting Law

• Timelines for Reporting
  – Clinical Trial Registries
    • Submission of information by latest of:
      – Date drug dispensed, administered, delivered or promoted in Maine
      – 21 days after patient enrollment
  – Clinical Trial Results
    • Submission of information by latest of:
      – Date drug dispensed, administered, delivered or promoted in Maine
      – 1 year (plus any extensions) after date on which trial was completed (i.e., final subject was examined or received intervention for purposes of final collection of data for primary outcome)
Federal Preemption of Maine Law

- **Maine Clinical Trials Registration and Results Reporting**
  - Food and Drug Administration Amendments Act of 2007 (FDAAA) requires clinical trial registration and results reporting
  - Maine acknowledges federal preemption of some reporting requirements but emphasizes need for compliance with state law pending issuance of final federal regulations implementing FDAAA requirements
  - Maine final regulations create correspondence with FDAAA
    - **Example:** Clinical trial results reporting
  - Maine does have broader reporting requirements
    - Reporting observational trials
    - Reporting of post-hoc analysis
    - Expanded registration information
      - Optional elements on clinicaltrials.gov
Overview of State Marketing Disclosure Laws

• Some similarities among laws – particularly later laws – but each has distinct requirements

• Key Issues
  – Scope/state law jurisdiction
    • Activity in state or interaction with health care provider licensed in state
  – Reporting entity
  – Other party to interaction
  – Reportable activity
  – Exceptions
  – Timing of disclosures
  – Confidentiality
# Overview of State Marketing Disclosure Laws

<table>
<thead>
<tr>
<th>State</th>
<th>CALIFORNIA</th>
<th>DISTRICT OF COLUMBIA</th>
<th>MAINE</th>
<th>MASSACHUSETTS</th>
<th>MINNESOTA</th>
<th>NEVADA</th>
<th>VERMONT</th>
<th>WEST VIRGINIA</th>
</tr>
</thead>
</table>

## Scope
- Pharmaceutical and medical device manufacturers
- Pharmaceutical manufacturers and labelers
- Pharmaceutical and medical device manufacturers
- Wholesale drug distributors, including drug manufacturers
- Pharmaceutical and medical device manufacturers
- Pharmaceutical manufacturers
- Pharmaceutical manufacturers and labelers

## Confidentiality of Information Submitted
- Not confidential. Submitted data is not easily searchable on a website.
- Confidential. Submitted identified data becomes public record in aggregate form provided the data does not reveal trade secrets.
- Confidential. Submitted identified data becomes public record in aggregate form provided the data does not reveal trade secrets.
- Not confidential. Submitted data will be easily searchable on a website.
- Not confidential. Submitted data is not easily searchable on a website.
- Not confidential. Protection for proprietary or confidential business information. Information concerning compliance is posted on website.
- Confidential. Submitted data becomes public information in aggregate form provided the data does not reveal trade secrets.

*Note that chart provided for general context and not intended to be relied on as a complete summary of state disclosure laws.*
# Overview of State Marketing Disclosure Laws

|---------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Threshold Values    | • Comprehensive compliance program                  | • Gifts and meals to practitioners of $25 or more per day plus anything provided at less than fair market value plus a range of expenses, including educational programs, consultant fees, travel and charitable grants | • Gifts and meals to health care providers and others of $25 or more per day plus anything provided at less than fair market value plus a range of expenses, including educational programs, consultant fees, travel and charitable grants | • Payments to/to practitioners and others of $50 or more per transaction in connection with sales and marketing activities (broadly defined) | • Payments to/to practitioners of $100 or more related to:  
  - Sponsorship of educational conference  
  - Honoraria for faculty at educational conference  
  - Compensation for consulting services in connection with genuine research project | • Marketing Code of Conduct and other compliance policies | • Payments of $25 or more made in connection with detailing, promotional, or other marketing activities to health care providers and others | • Aggregate reporting for payments under $25 |
| Some Exceptions to | • None (specific payments not disclosed)             | • Reasonable support of bona-fide clinical trials  
  - Limited student/trainee scholarships and sponsorships for conference attendance  
  - Free product samples provided for patients | • Reasonable support of bona fide clinical trials  
  - Limited student/trainee scholarships and sponsorships for conference attendance  
  - Free product samples provided for patients | • Clinical trials and genuine research  
  • Demonstration or evaluation units  
  • In-kind items used for the provision of charity care  
  • Discounts  
  • Royalties and licensing fees  
  • Free product samples provided for patients | • Clinical trial compensation is not exempted from disclosure | • None (specific payments not disclosed) | • Reasonable support of bona-fide clinical trials  
  - Discounts  
  - Royalties and licensing fees | • Reasonable support of bona-fide clinical trials  
  - Limited student/trainee scholarships and sponsorships for conference attendance  
  - Free product samples provided for patients |
| Required Disclosures| • None (specific payments not disclosed)             | • Reasonable support of bona-fide clinical trials  
  - Limited student/trainee scholarships and sponsorships for conference attendance  
  - Free product samples provided for patients | • Reasonable support of bona fide clinical trials  
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  - Limited student/trainee scholarships and sponsorships for conference attendance  
  - Free product samples provided for patients |

*Note that chart provided for general context and not intended to be relied on as a complete summary of state disclosure laws.*
Overview State Marketing Disclosure Laws

State Reporting Timelines

April 1
Maine
(1) Clinical Trial and Advertising Regulations
(2) Clinical Trial Disclosure Regulations

May 1
Minnesota
Report Due

June 1
Nevada
Marketing Code of Conduct Report Due

July 1
District of Columbia
Marketing Costs Report Due

Maine
Marketing Costs Report Due

Massachusetts
Marketing Report Due

October 1
Vermont
Chief Compliance Officer Form

November 1
Vermont
Marketing Disclosure Report Due

Annual Reports (No Specific Date Provided):

California
Comprehensive Compliance Program Annual Declaration Posting

ROPES & GRAY
## State Marketing Disclosure Laws: Treatment of Clinical Trials

<table>
<thead>
<tr>
<th>State</th>
<th>Clinical Trial Research</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>Not applicable</td>
<td>No direct treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note that payments for legitimate professional services (if fair market value and conform with the OIG Voluntary Compliance Guidance for Pharmaceutical Manufacturers and the PhRMA Code) are excluded from annual aggregate spend limits</td>
</tr>
<tr>
<td>District of Columbia</td>
<td>No definition of “bona fide clinical trial”</td>
<td>No reporting of reasonable compensation for expenses in connection with a “bona fide clinical trial” of a new vaccine, therapy or treatment</td>
</tr>
<tr>
<td>Maine</td>
<td>“Bona fide clinical trial” means any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause and effect relationship between a medical intervention and a health outcome.</td>
<td>No reporting of reasonable compensation and reimbursement for expenses in connection with a “bona fide clinical trial” of a new vaccine, therapy, or treatment</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>“Clinical trial” means a genuine research project involving a drug or medical device that evaluates the safety or effectiveness of the particular drug or biologic in the screening, prevention, diagnosis, evaluation or treatment of a disease or health condition, or evaluates the safety or efficacy of the drug in comparison with other therapies, and which has been approved by the FDA and, if the trial involves volunteer human research subjects, it has been approved by an IRB. “Genuine Research Project” means a project intended to add to medical knowledge about the care and treatment of patients that constitutes a systematic investigation, designed to develop or contribute to generalizable knowledge when the results can be published by the investigator and reasonably can be considered to be of significant interest or value to scientists or health care practitioners working in the particular field of inquiry.</td>
<td>No reporting of payments in connection with “clinical trials” (other than post-marketing clinical trials) and “genuine research” Reporting exclusion includes payments in conjunction with pre-clinical trials as long as the payments are related to the design and development of a clinical trial</td>
</tr>
</tbody>
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## State Marketing Disclosure Laws: Treatment of Clinical Trials

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<th>Treatment</th>
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<tbody>
<tr>
<td>Minnesota</td>
<td>Genuine research project (undefined)</td>
<td>Reporting of compensation (including meals) for the substantial professional or consulting services of a practitioner in connection with a genuine research project.</td>
</tr>
<tr>
<td>Nevada</td>
<td>Not applicable</td>
<td>No direct treatment</td>
</tr>
<tr>
<td>Vermont</td>
<td>A “clinical trial” is any study assessing the safety or efficacy of prescribed products administered alone or in combination with other prescribed products or other therapies, or assessing the relative safety or efficacy of prescribed products in comparison with other prescribed products or other therapies. A “bona fide clinical trial” includes only a FDA-reviewed clinical trial that constitutes “research” as that term is defined in 45 C.F.R. § 46.102 (HHS Common Rule), and reasonably can be considered to be of interest to scientists or health care professionals working in the particular field of inquiry</td>
<td>Reporting for a “bona fide clinical trial” of: (1) gross compensation for the Vermont location(s) involved; (2) direct salary support per principal investigator and other health care professionals per year; and (3) expenses paid on behalf of paid reviewers. Reporting a research project that can reasonably be considered of significant interest or value to scientists or health care professionals in field of inquiry: (1) gross compensation; and (2) direct salary support and expenses paid per health care professional Delayed reporting of payments for clinical trials until the earlier of FDA approval or clearance of the prescribed product or two calendar years from the payment date. During delay period, manufacturer must still disclose, at the close of the fiscal year in which the trial began, the clinical trial name, its start date, and the web link to the clinical trial registration on the national clinical trials registry.</td>
</tr>
</tbody>
</table>

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### State Marketing Disclosure Laws: Treatment of Clinical Trials

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</tr>
</thead>
<tbody>
<tr>
<td>West Virginia</td>
<td>“Bona-fide clinical trial” means a clinical trial approved by an institutional review board in compliance with the statutory and regulatory requirements of the FDA, including Title 21 of the United States Code, 21 C.F.R., Part 56 and 45 C.F.R. § 46.101, and conducted in connection with a research study the principle purpose of which is scientific research. “Clinical trial” means an approved clinical trial conducted in connection with a research study designed to answer specific questions about vaccines, new therapies or new ways of using known treatments.</td>
<td>No reporting of payments of reasonable compensation and reimbursement of expenses in connection with a “bona-fide clinical trial”</td>
</tr>
</tbody>
</table>

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Federal “Sunshine” Provisions (Section 6002 of Patent Protection and Affordable Care Act)

- Effective for payments or other transfers of value on or after January 1, 2012
- Requires reporting by “applicable manufacturers” to “covered recipients” of payments related to research on new technology or new drug, device or biologic
  - Information confidential until public posting on earlier of (1) FDA approval or clearance date or (2) 4 years after payment date
Federal Preemption of State Laws

- Preemption of state law (or portion of state law) that requires disclosure “in any format” of information required to be reported under federal law
- Preemption expressly not comprehensive
- First report due March 31, 2013 for prior calendar year
Federal Preemption of State Laws

- **No** preemption of state law (or portion of state law) that requires disclosure of information:
  - Other than by “applicable manufacturer” to “covered recipient”
  - Physician or teaching hospital
  - Other than information reported under federal law
    - States *can* require reporting of information *exempt* under the federal law *other than* transfers of value less than $10 per transfer
    - To government agency for public health purposes
  - No limit on discovery or admissibility of information in criminal, civil or administrative proceeding
Impact of Federal Preemption on State Marketing Disclosure Laws

• Reporting Entity
  – Maine and Vermont require reporting by “labelers”

• Non-Physician or Teaching Hospital Recipients
  – District of Columbia, Maine and Minnesota include non-physician practitioners
  – Massachusetts and Vermont include class of even broader health care providers
    • Massachusetts: Individuals and entities that prescribe, dispense or purchase prescription drugs and devices in state
    • Vermont: Healthcare professional (prescriber) and other individuals and entities authorized to dispense or purchase for distribution prescribed products in state
Impact of Federal Preemption on State Marketing Disclosure Laws

• Clinical Trial Information
  – Clinical trial and product research information preempted
  – Consider scope of clinical trial/research information
    • Post-marketing clinical trials
    • Research conducted under grants for investigation-initiated clinical research
    • Consider timing issues
    • Overlap in federal and state reporting periods in 2012
Clinical Trials: Promoting Transparency

Letting the Sunshine [Act] In!

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Presentation Overview

- Physician Payment Sunshine Provisions of Patient Protection & Affordable Care Act
- Other Transparency Regulations on the Horizon:
  - FDA Proposed Regulation on Reporting Possible Data Falsification
  - HHS Proposed Financial Conflict of Interest Regulations — Promoting Objectivity in Research”
Act’s Effective Dates

- §6002 Transparency Reports & Reporting of Physician Ownership or Investment Interests
  - Effective Date for Recording Transfers of Value – 1/1/12
  - Effective Date for Reporting to HHS -- 3/31/13
  - Date for Publication of First Report – 9/30/13 and June 30th of each year thereafter
Act’s Requirements– Payments or Transfers of Value

- Who Must Record/Report: Group Purchasing Organizations and Manufacturers of “covered drug, device, biological, or medical supply”
Act’s Requirements– Payments or Transfers of Value

- What Must be Recorded/Reported:
  - Payment or transfer of value to Covered Recipient
  - Cash, in-kind, stock or other ownership interest, any other form of payment
  - Includes: consulting fees; compensation for services; honoraria; gifts; entertainment; food; travel; education; research; charitable contributions; royalty or license; current or prospective ownership or investment interest; direct compensation for serving as faculty/speaker for medical education program; grant; any other payment or transfer of value as defined by HHS Secretary to a covered recipient"
Act’s Requirements– Physician Ownership/Investment Interests

- What Must be Recorded/Reported:
  - Physician Ownership or Investment Interest: Ownership or investment interest, other than interest in publicly traded security or mutual fund, held by physician or immediate family member in manufacturer or group purchasing organization.
Act’s Requirements – “Covered Recipient”

- “Covered Recipient” =
  - Physician; Teaching Hospital
  - Excludes physician who is an employee of the manufacturer who is required to submit the report.
Exclusions

- Not included in Payment or Other Transfer of Value:
  - <$10 unless aggregate/calendar yr. > $100
  - Product samples for patient use
  - Educational materials that directly benefit patients or are intended for patient use
  - Short-term loan of covered device
  - Items/services provided under contractual warranty
  - Transfer to covered recipient acting in capacity of patient
  - Discounts/rebates
  - In-kind items used for charity care
  - Dividend from interest in publicly traded security/mutual fund
  - Health care payments under self-insured plans
  - Transfers to licensed non-medical professionals for non-medical professional services
  - Transfer for payment for service re. civil, criminal or administrative action
Product Development and Clinical Investigations Payments: Report payments for services provides in connection with development of or clinical investigation re. drug/device/biologic/medical supply on earlier of (a) date of approval/clearance of drug/device or (b) 4 yrs. after payment is made.
Information Reported

- Name of covered recipient
- Business address/specialty/National Provider ID
- Amount and date of payment
- Description of form, e.g., cash, stock, etc.
- Description of nature, e.g., consulting fee, etc.
- If payment is related to drug/device/supply–specific mkt., education, or research – name of drug/device/supply.
- Any other categories of info specified by HHS Secretary.
Impact on State Laws

- Preemption of State law “that requires an applicable manufacturer to disclose or report in any format the type of information . . . [the Act] requires regarding such payment or transfer of value.”
- BUT, no preemption of additional State law requirements.
Will it Achieve Transparency?

- Implementation Issues – multiple databases
- Requires disclosure, not limitation
- BUT limitations imposed by:
  - Some state laws
  - Many academic medical centers
  - Will information collected under the Act be used to identify non-compliance with state laws or institutional requirements?
FDA Proposed Reg. on Possible Falsification of Data

- 75 Federal Register 7412, Feb. 19, 2010
- Comment Period ended May 20, 2010
- Effective Date – 90 days after publication of final rule
FDA Proposed Reg. on Possible Falsification of Data

- How does FDA currently handle reports of scientific misconduct?
  - 21 CFR 312.56(b)
  - Sponsor must
    - Secure compliance with 1572; or
    - Stop investigator’s participation and report to FDA
  - Consequences to Investigator for reporting false data to Sponsor
  - Consequences to Sponsor for reporting false data to FDA
FDA Proposed Reg. on Possible Falsification of Data

- Proposed Rule:
  - Sponsor must report to FDA within 45 days after becoming aware of information that:
    - Any person **has, or may have**, engaged in the falsification of data
      - In reporting study results
      - In proposing or designing research
      - In supervising or reviewing studies conducted for sponsor or on which sponsor relies
FDA Proposed Reg. on Possible Falsification of Data

Definition of “Falsification of Data”
- Data changed so they don’t represent what actually happened
- Data created for events that never happened
- Data altered
- Data recorded or altered in a way that doesn’t reflect what happened
- Omitted data
FDA Proposed Reg. on Possible Falsification of Data

- “Has or may have” standard
- No evidence of intent necessary, although “errors” such as typos and transposed numbers are excluded
- No investigation required to
  - Determine if data was definitively falsified
  - If person suspected of falsification had any intent to do so
FDA Proposed Reg. on Possible Falsification of Data

- Food for Thought
  - Covers everyone involved in study, e.g., coordinators, lab techs, etc.
  - On-going requirement – applies before study starts and after study ends
  - How will it work with NSF and PHS rules on research misconduct?
  - IRB reporting?
  - Ambiguous reports.
HHS Proposed Financial Conflict of Interest Regulations

- Regulations for “Promoting Objectivity in Research” issued by the Department of Health and Human Services
  - Regulations for Grant Recipients -- Title 42 Code of Federal Regulations, Part 50, Subpart F, Section 50.601–50.607
  - Regulations for Contractors – Title 45 Code of Federal Regulations, Part 94, Sections 94.1 to 94.6
- Current Status – OMB review
HHS Proposed Financial Conflict of Interest Regulations

- Major Change = Definition of “Significant Financial Interest”
- “A financial interest consisting of one or more financial interests of the Investigator (or of his/her spouse or dependent children) that reasonably appears to be related to the investigator’s Institutional Responsibilities.”
  - Lists types of financial interests
  - Monetary threshold dependent on type of interest.
HHS Proposed Financial Conflict of Interest Regulations

- Significant Financial Interest EXCLUDES:
  - Salary, royalties or other remuneration paid by the Institution to the Investigator if the Investigator is currently employed or otherwise appointed by the Institution.
  - Any ownership interest held by the Investigator in the Institution if the Institution is a commercial or for-profit organization.
  - Income from seminars, lectures, or teaching engagements sponsored by a federal, state or local government agency or an institution of higher education.
  - Income from service on an advisory committee or review panel for a federal state or local government agency or an “institution of higher education.”
HHS Proposed Financial Conflict of Interest Regulations

- WATCH OUT FOR PROPOSED REGULATIONS CHANGE IN MONETARY THRESHOLDS
  - Current Regulation -- $10,000 or not more than 5% ownership interest in a single entity.
  - Proposed Regulation – Lowers threshold to $5,000 or eliminates it altogether for some interests.
    - Publicly traded v. non–publicly traded entity
HHS Proposed Financial Conflict of Interest Regulations

- Current Process Overview
  - Investigator discloses when he/she submits funding application.
  - Investigator discloses Significant Financial Interests (over $10,000 or 5% equity) that Investigator determines:
    - Would reasonably appear to affect the research; or
    - Are in an entity that reasonably would appear to be affected by the research.
  - Updates of interests are required.
  - Institution determines if there is “conflicting interest” and whether it can be managed, reduced or eliminated.
Proposed Process Overview -- Disclosures

- Institution obtains original disclosure of Significant Financial Interests from investigator when he/she is planning to participate in PHS–funded research.
- Institution obtains annual updates for Investigators participating in PHS–funded research.
- Institution obtains ad hoc disclosure for new Significant Financial Interests.
- Look at interest aggregated over preceding 12 months.
HHS Proposed Financial Conflict of Interest Regulations

- Additional institutional responsibilities under proposed regulations:
  - Written, published policy
  - Mandatory training
  - Publication of Disclosures on the Web – Before expending any PHS funds on a research project, the Institution must post on publicly accessible website information about any currently held Significant Financial Interest that constitutes a Financial Conflict of Interest for any Investigator who serves as senior or key personnel on an PHS funded project or proposed project.
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Corporate Integrity Agreements (“CIAs”): Recent Examples

- Forest Labs
- Novartis Pharmaceutical Corporation
- Allergan Inc.
- Synthes
Allegations Against Forest, 2010, Celexa (citalopram), Lexapro (escitalopram), Anti-depressants

- Fifty-four lawsuits, mostly involving teens’ suicides and attempted suicides
- Accuse Forest of:
  - Concealing a negative pediatric study on Celexa
  - Misleading physicians about the drug's clinical trials
  - Targeting children in promotions of Celexa and Lexapro
Prior to the Effective Date, Forest implemented written P&P regarding the operation of the Compliance Program and Forest’s compliance with Federal health care program and FDA requirements (P&P). To the extent not already accomplished, within 120 days after the Effective Date, Forest shall ensure that the P&P address or shall continue to address:

- q. sponsorship of post-marketing clinical studies or other post-marketing studies, including investigator-initiated trials (IITs), relating to Government Reimbursed Products, including the decision to provide financial or other support for the IITs; the manner in which such support is provided; and support for publication of information about the IITs, including the publication of information about the trial outcomes and results and the uses made of publications relating to IITs.
Allegations Against Novartis, 2010

- Off-label promotion of Trileptal (Rx epilepsy) for bipolar disorder and neuropathic pain; five other drugs - Diovan, Zelnorm, Sandostatin, Exforge and Tekturna
- Paying kickbacks to health care professionals to induce them to prescribe these drugs
- Deal:
  - $422.5 M: $237 M to settle four whistleblower lawsuits; $185 M for criminal penalties
  - Monetary penalties for less significant breaches
  - CIA; can be excluded from federal health care programs for a material breach
Within 120 days after the Effective Date, Novartis shall register all clinical studies and report results...on...www.clinicaltrials.gov...Novartis shall continue to comply with [all] applicable requirements relating to the registration and results reporting of clinical studies throughout the term of this CIA...[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...Novartis shall fully comply...
• To the extent not already accomplished, within 120 days after the Effective Date, Novartis shall ensure that the P&P address or shall continue to address:…
  – s. sponsorship of post-marketing research and investigator-sponsored studies (ISSs) (sometimes also called investigator-initiated trials) including the decision to provide financial or other support for the ISSs;…and support for publication of information about the ISSs, including the publication of information about the trial outcomes and results and the uses made of publications relating to ISSs…
Specifically, the IRO shall review Novartis’ systems, processes, policies, and procedures associated with the following (hereafter “Reviewed P&P”): …

- 10) Novartis’ systems, processes, policies, and procedures relating to investigator-initiated studies (ISSs) including the decision to provide financial or other support for those studies; …and support for publication of the information about those studies, including publication of information about the trial outcomes and results and the uses made of publications relating to those studies.
Allergan: Botox Allegations

- Used cervical dystonia indication to ↑ off-label sales
  - Claimed CD was “underdiagnosed”
- Workshops to teach docs how to bill for off-label uses
- Audited docs’ billing records to show how they could make money by injecting Botox®
- Operated Reimbursement Hotline (free to docs)
- Lobbied health care programs to expand coverage
- Paid docs to attend “advisory boards” promoting off-label uses
- Created online neurotoxin education organization
To the extent not already accomplished, within 150 days after the Effective Date, Allergan shall ensure that the P&P address or shall continue to address:…

- the sponsorship of post-marketing clinical trials or other post-marketing studies (including IITs) including the decision to provide financial or other support for such studies;…and support for publication of information about such studies, including the publication of information about the trial outcomes and results and the uses made of publications relating to such studies…
Allergan CIA: Trial Registration

- Allergan represents that for all applicable clinical trials...where Allergan is a sponsor, it registers and reports the results on ...www.clinicaltrials.gov or requires that another responsible party...register and report the results...Allergan shall continue to comply with [all] applicable requirements relating to the reporting of clinical study information throughout the term of this CIA. In addition, if there is a change in Federal health care program requirements, FDA requirements, or other applicable requirements relating to the reporting of clinical study information, Allergan shall fully comply with such requirements...
Specifically, the IRO shall review Allergan’s systems, processes, policies, and procedures associated with the following (hereafter “Reviewed P&P”): …

- 10) Allergan’s systems, processes, P&P relating to [IITs] including the decision to provide financial or other support for those studies; the manner in which support is provided for the IITs; and support for publication of the information about those studies, including publication of information about the trial outcomes and results and the uses made of publications relating to those studies;…
Synthes Allegations

- Norian conspired with Synthes in unauthorized trials of Synthes devices in surgery for spinal vertebral compression fx (VCFs)
- Risks:
  - Label warning for Norian XR against this use
  - Safety issues when device used in the spine
- Before marketing began, pilot studies showed:
  - Bone cement reacted with blood *in vitro* to cause blood clots
  - Pig: Pulmonary emboli ensued
- Marketed product for VCFs anyway, without testing it
- Kept marketing product until 3 patients died
- Carried out a cover-up; made false statements to FDA during official inspections in 2004
Synthes CIA

- Norian’s parent, Synthes, will sell all Norian assets within a limited period of time
  - If Synthes fails to comply, OIG-HHS will exclude Norian
- Five-year CIA with OIG-HHS requiring Synthes to implement a compliance program designed to minimize future improper conduct
• To the extent not already completed, within 120 days after the Effective Date, Synthes shall implement written P&P regarding… operation of the Compliance Program and Synthes' compliance with Federal health care program and FDA requirements (P&P). At a minimum, the P&P will address the following: …
  – sponsorship, funding of, and disclosures relating to research and development-related activities (including clinical trials, test markets, market research, and authorship of articles and other publications). These P&P shall be designed to ensure that Synthes' funding and/or sponsorship complies with all applicable Federal health care program and FDA requirements…
Foreign Trials
The Rise of Foreign Trials

- Opportunity to aid those with limited healthcare
- Lower costs
- Diminished liability exposure
- Fewer regulatory complexities
- Global market; harmonization of U.S., European, and Japanese drug evaluation procedures
  - Opportunity to seek regulatory approval in various national markets simultaneously
- CROs
The Impetus for Registration of Foreign/International Trials

• ICMJE (and WHO): Register all interventional studies in humans regardless of intervention type
  – 20-item minimum dataset
  – Must register at or before onset of patient enrolment
  – Prerequisite for publication in peer-reviewed journals
  – Registry to be searchable, freely accessible to public, open to all registrants, managed by a non-profit
  – N/A observational studies

• WHO promotes information on new clinical studies to be registered in national primary registers
  – Language?
WHO’s International Clinical Trial Registry Platform (“ICTRP”)

- Not itself a registry, but a network of registries
- **Primary registers**: WHO-selected
  - Managed by not-for-profit entities
  - Accept any interventional trials; delete duplicates
  - Provide data directly to WHO
  - Australian New Zealand Clinical Trials Registry, Chinese Clinical Trials registry, Clinical Trails Registry—India, The Netherlands National Trial Register, Sri Lanka Clinical Trials Registry
- **Partner registers**: more numerous
  - Include registers that submit data to primary registers but limit their own register to trials in a restricted area
    - Specific disease, company, academic institution, or geographic region
Mandatory Registration of New Clinical Trials in National Public Registers

- Argentina, Brazil, Croatia, Czech Republic, France, India, Israel, Italy, South Africa, U.S., Taiwan
  - Only the U.S. requires results disclosure for completed studies
- Often in the national language (e.g. Japan, Taiwan)
- But may choose to use existing infrastructure in another country to support registration needs (Israel)
- Often to have the product registered in a given country, must undertake trials in that country
- Can require registration for ethics approval
Voluntary Registration

- Often incomplete
- National guidance: Africa (Pan-African registry), Australia, China, Cuba, Germany, Japan, New Zealand, Spain, Sri Lanka, UK
Problems with Existing System

- Many registers available
- Multiple entries of the same clinical trial in different registers
- Inconsistent requirements
  - Timelines
  - Excluded trials
  - Required data, etc.