Managing Conflicts of Interest and Attorney Ethics in Research Relationships Between Industry and Healthcare Entities

New York State Bar Association, Health Law Section
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NYSBA

Hypothetical Case

- ☐ Dr. Smith is an Investigator at A me University Medical Center on a DrugCo-s red tri the drug "Ha Pill"
- ☐ "Happy Pill" w Dr. Jones and t
- ☐ The CE
- ☐ Dr.
- ☐ 6 began working as Drug or speaker pro earning 25,001/year

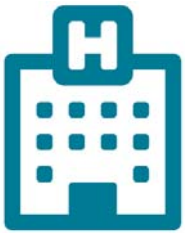
Should any financial interests have been disclosed here? To whom? Is a Research Conflict Management Plan needed? Should any aspect be disallowed?

What is the concern?

Financial relationships in research may raise concerns about bias and conflict of interest, potentially putting human subjects at risk and undermining scientific integrity

Individual Conflict- Financial interests of HCPs, Investigators, research staff etc.

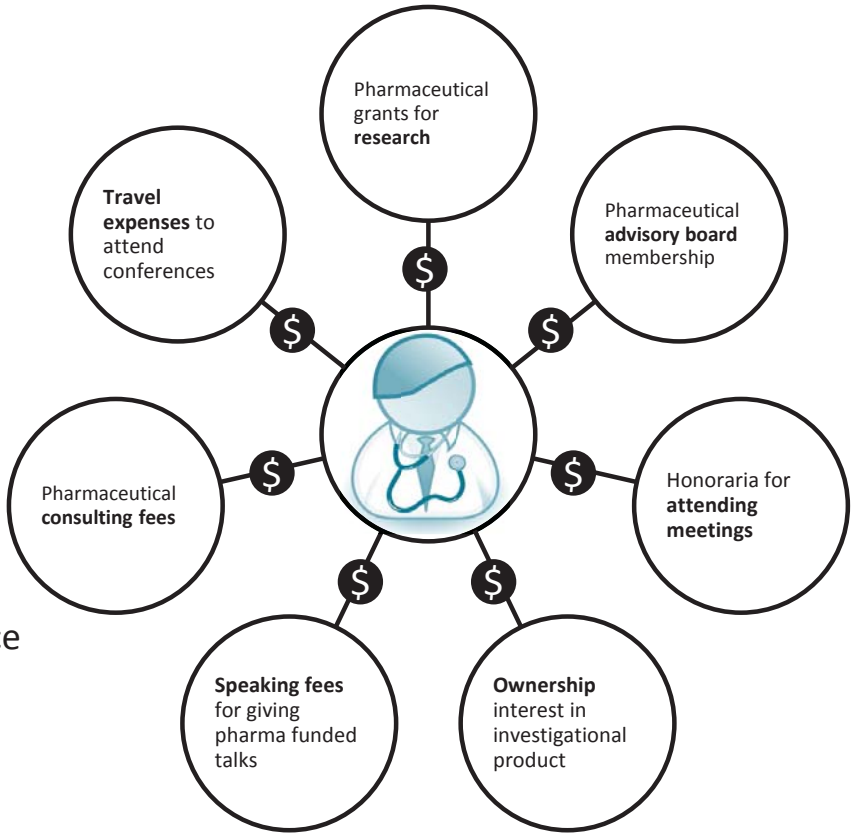
Institutional Conflict- Financial interests of university, hospital, or senior officials



Individual Financial Conflict

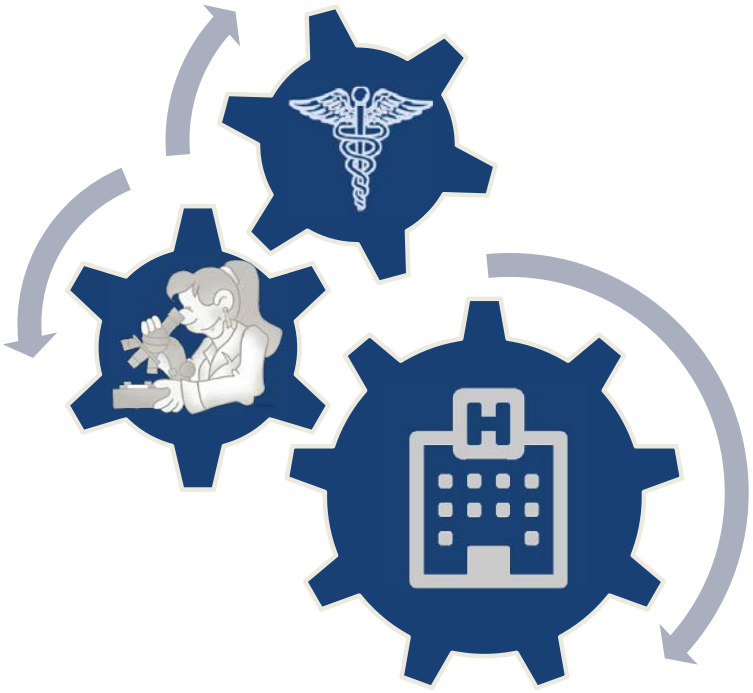
Examples of Potential Investigator Financial Conflicts (and includes immediate family of investigator):

- ☐ Equity interest in the study sponsor (e.g. stock or stock options)
- ☐ Compensation linked to future product sales (e.g. a royalty interest)
- ☐ Research grant/gifts
- ☐ Equipment from sponsor
- ☐ Board membership on study sponsor
- ☐ Paid professional consulting/SAB service
- ☐ Explicitly higher compensation for a favorable study outcome



Institutional Financial Conflict

- FCOI arise when **an institution's own financial interests or those of its senior officials pose risks of undue influence on decisions**
- HHS: "C*areful consideration is necessary before PHS regulations could be formulated that would address the subject of institutional conflict of interest in the same comprehensive manner as the 1995 regulations address Investigator FCOI.*"
  - **no consensus on a definition exists**
- Most AMCs and universities treat licensing fees, royalties, and equity interests as FCOIs
- Routine clinical trial fees/service reimbursements are not considered conflicts, as reflected in 21 §CFR 54



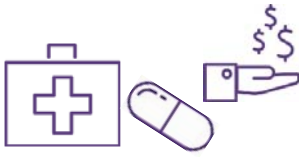
***Source**: Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice; 76 FR 53255*

Why Are There More Financial Conflicts?

Traditional research Model

Government Funding

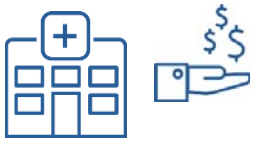
Lab Invention by Dr. #1 at Academic Medical Center #1



Licensed to Pharma Co.

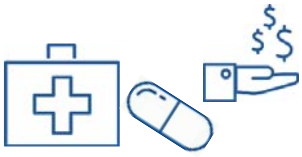
Clinical Trial at Academic Medical Center #2 with Dr. #2

Evolving Research Model



Academic Medical Center Funding

Lab Invention by Dr. #1



Licensed to AMC Spinoff Co. which pays for Clinical Trial

Clinical Trial at same Medical Center by Dr. #2

Pharma Co. hires Dr. #2 as consultant

Financial Conflict Disclosure Obligations

Who discloses, to whom and how?

- **Principal Investigator**
  - IRB & Institution — *Institutional Policy*
  - Pharma Sponsor — *FDA Form 3455*
  - Medical Journals — *ICMJE Form*
  - Research Subject — *Informed Consent*
- **Institution**
  - NIH — *42 CFR 50*
  - Research Subject — *Informed Consent*
- **Pharma Companies**
  - FDA — *FDA Forms 3454/3455*
  - CMS — *Open Payments*

FDA Financial Disclosure Requirements

Scope of the law

- ☐ Investigators must disclose financial conflicts on FDA regulated clinical trials (**21 CFR §54.3**)

Whose financial interests?

- ☐ All clinical investigators directly involved in the treatment or evaluation of research subjects (**21 CFR §54.2(d)**)
- ☐ Investigators' spouses and dependent children

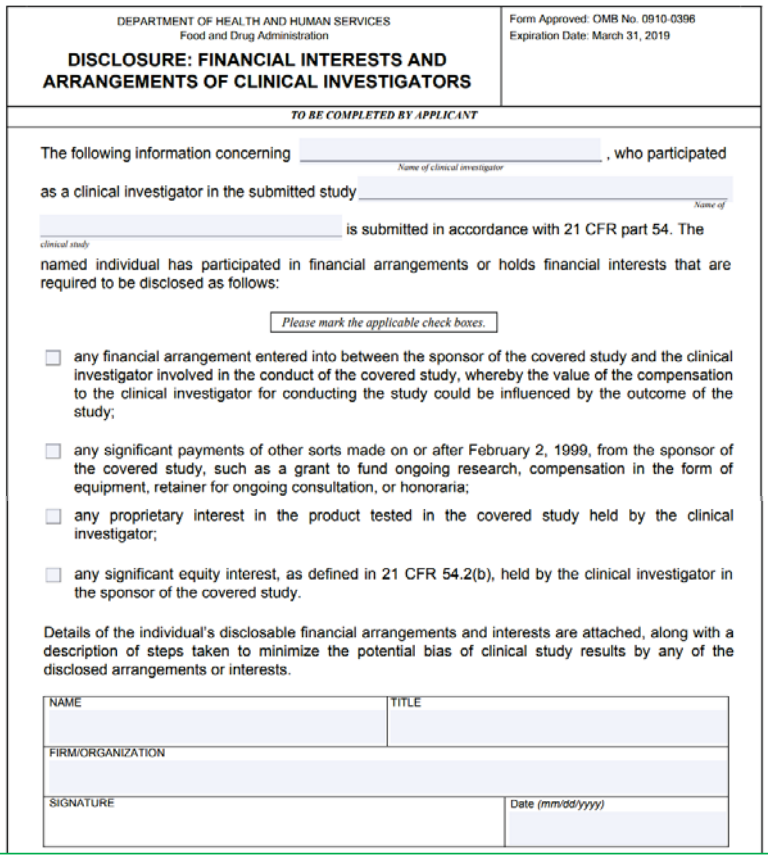
Which interests require disclosure?

- ☐ Any financial arrangements where the study outcome can influence PI's compensation
- ☐ "*Significant payments of other sorts*" from industry to support the activities of the investigator that exceed **$25,000** in value, excluding the cost of conducting the study, received during the study and for 1 year after study completion
- ☐ Proprietary interest in tested product
- ☐ Equity interest in sponsor exceeding **$50,000** in value, during the study and for 1 year after study completion

FDA Financial Disclosure Form

Requirements

- ☐ ***Submit a certification*** attesting to an absence of financial interests or a ***disclosure statement*** delineating the financial interests for relevant clinical investigators **(21 CFR § 54.4)**
- ☐ Certification/disclosure is reportable as an element of a study sponsor's drug marketing application to the FDA



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

The following information concerning _____ (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study _____ (*Name of clinical study*) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

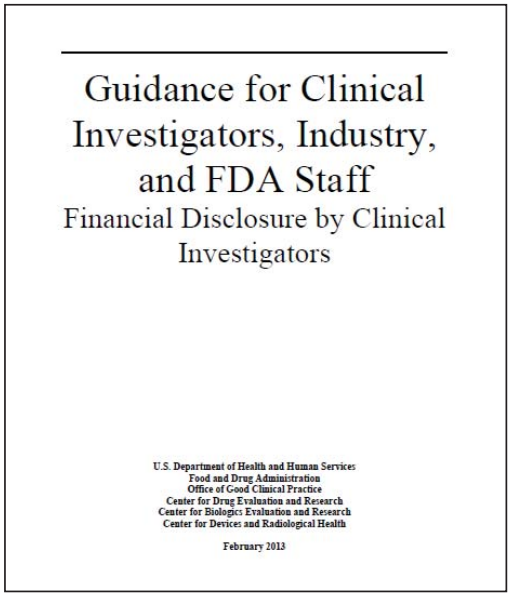
☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	Date (*mm/dd/yyyy*)

FDA Guidance on Managing Conflicts

- "FDA's review of clinical investigator financial disclosure information alerts FDA staff to financial interests and arrangements that could lead to bias in covered clinical studies."
- "The financial disclosure process also provides FDA with information regarding whether and to what extent the sponsors have taken steps to minimize the risk of bias."
- "An important means of minimizing the potential for bias resulting from such financial interests and arrangements is through proper study design (see 21 CFR § 54.5(b)). **For example, using randomization and blinding helps to minimize the potential for bias in assigning subjects to receive the test article or placebo and in assessing study outcomes and analyzing results."**


Guidance for Clinical Investigators, Industry, and FDA Staff

Financial Disclosure by Clinical Investigators

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

February 2013

***Source**: FDA Financial Conflict of Interest Guidance, 2013*

NIH Financial Disclosure Requirements

Scope of the law

- ☐ Investigators participating in ***Public Health Service funded research*** (i.e. recipients of NIH grants) must disclose "significant" financial interests to their institution

Whose financial interests?

- ☐ The project director/principal investigator and anyone responsible for the design, conduct, or reporting of research **(42 CFR §50.603)**

When are financial interests "significant"?

- ☐ Remuneration from a publicly traded company received in the 12 months before disclosure + value held in equity at time of disclosure, if this sum exceeds **$5,000**
- ☐ Remuneration from a non-publicly traded company received in the 12 months before disclosure if the value exceeds **$5,000**, or any equity interest held in the entity
- ☐ Intellectual property interests, once related income is received

Who and What is Covered?

- ☐ The regulations apply to individual FCOIs, but impose obligations on both individuals and institutions who apply for or receive NIH research funding

NIH Financial Disclosure Requirements

Requirements for institutions

- ☐ Implement a Financial Conflicts policy and post it on Institution's website (**42 CFR §50.604(a)**)
- ☐ Provide FCOI reports to the PHS Awarding Component (**42 CFR §50.604(a)**)
- ☐ Require investigators participating in PHS-funded projects to disclose their significant conflicts of interest (**42 CFR §50.604(e)(1)**)

Requirements for investigators

- ☐ Disclose any reimbursed or sponsored travel related to their institutional responsibilities (**42 CFR §50.603**)
- ☐ Not applicable to travel reimbursed/sponsored by a government or higher education institution, including academic teaching hospitals, medical centers, and affiliated research institutes

HHS Office for Human Research Protection (OHRP) Guidance

Points for Consideration

- ☐ Does the research involve financial relationships that could create potential or actual conflicts of interest?
- ☐ How should financial relationships that potentially create a conflict of interest be managed?

Actions to Consider

- ☐ Establishing independence of institutional responsibility for research activities from the management of institution's financial interests.
- ☐ Establishing procedures for disclosure of institutional financial relationships to COICs.

- ☐ Including individuals from outside the institution in the review and oversight of financial interests in research.
- ☐ Using independent organizations to hold or administer the institution's financial interest.

Source: *HHS Guidance for Financial Conflicts of Interest, 2004*

Government Enforcement Powers

FDA may respond to financial conflict of interest in the following ways:

- ☐ Audit data from the investigator in question
- ☐ Request further data analysis from the applicant
- ☐ Request additional independent studies be conducted by applicant
- ☐ **Decline to recognize the questioned study**

NIH may respond to unreported FCOI in the following ways:

- ☐ Refer the matter to the institution
- ☐ Impose specific award conditions
- ☐ Suspend funding
- ☐ Require the investigator to disclose the FCOI in each public presentation of the research results and to request an addendum to previously published presentations

***Source**: FDA Financial Conflict of Interest Guidance, 2013; 21 CFR 54.5*

Medical Journal Conflict Disclosure

ICMJE Form for Disclosure of Potential Conflicts of Interest

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

Conflict Management Plan Examples

Reporting Obligation to Institution

☐ "In order to manage any real or perceived Conflicts of Interest, you agree to disclose promptly on the *Investigator's Statement of External Interests* any research, administrative, and/or consulting activities you perform for the Company"

Institutional Oversight of PI

☐ "Use of Laboratory space normally under the supervision of the Applicant will be supervised by the Management Plan Monitor."

☐ "Management Plan Monitor shall retain fiduciary oversight for the contract (e.g. review and authorization of expenditures… and other fiscal and administrative tasks)."

Restrictions on Enrolling Research Subjects

☐ You may not serve as "Consenting Professional" to enroll subjects in the study.

Disclosure to Colleagues

☐ "[Faculty] Member will disclose, in writing, information about all actual, potential, and perceived conflicts of interest arising from their relationship with Outside Entity to all students and staff whom they supervise in the course of the Project."

Disclosure to Research Subjects- Informed consent

***Source**: Conflicts of Interest Management Plan, University of Georgia; Conflict of Interest Management Plan Template, Washington State University; Conflicts of Interest Management Plan, University of Notre Dame*

Research Consent Disclosure of FCOI

Template language to disclose individual conflicts:

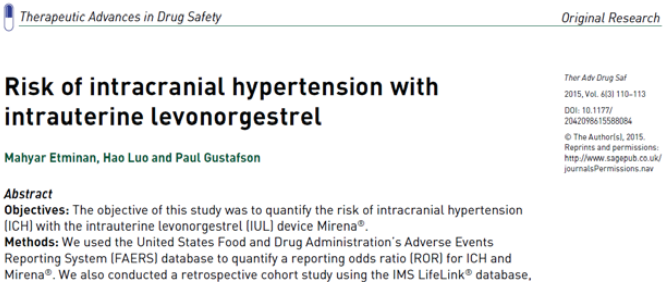
- ☐ "The investigator, **Dr. (full name), owns [equity or stock] of the company that is paying for the research**."
- ☐ "The investigator, **Dr. (full name), personally receives consulting or other payments from the company that is paying for the research**."
- ☐ "The investigator, **Dr. (full name), is an inventor of the [drug, compound, device, etc.], for which a patent may be filed by the institution. If the patent is pursued, based on data from this and other research, royalties and other compensation may be received by the institution and the investigator**."

Template language to disclose institutional conflicts:

- ☐ "This study is paid for by [name of sponsor] which owns the {drug} or {device} being tested and thus has a financial interest in the outcome of the study. **Payments are made to Institution and the funds are used to cover the expenses of the study and related academic and research activities of the institution**."
- ☐ "The **Institution owns stock in the company that is paying for this study**."

***Source**: Weill Cornell Medical College, Office of Research Integrity, Conflicts Management Office*

Research Conflict Meets *Daubert*



Therapeutic Advances in Drug Safety — *Original Research*

Risk of intracranial hypertension with intrauterine levonorgestrel

Ther Adv Drug Saf
2015, Vol. 6(3) 110–113
DOI: 10.1177/2042098615588084
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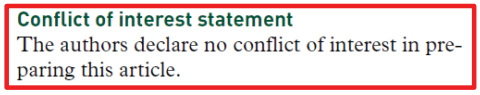
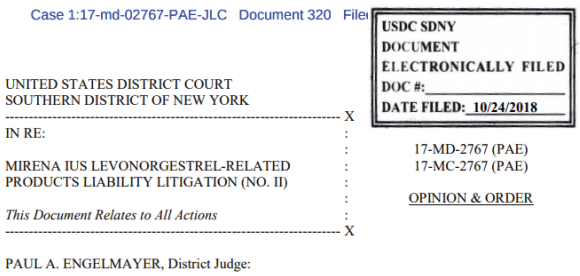
Mahyar Etminan, Hao Luo and Paul Gustafson

Abstract
Objectives: The objective of this study was to quantify the risk of intracranial hypertension (ICH) with the intrauterine levonorgestrel (IUL) device Mirena®.
Methods: We used the United States Food and Drug Administration's Adverse Events Reporting System (FAERS) database to quantify a reporting odds ratio (ROR) for ICH and Mirena®. We also conducted a retrospective cohort study using the IMS LifeLink® database,



Conflict of interest statement
The authors declare no conflict of interest in preparing this article.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.



Case 1:17-md-02767-PAE-JLC Document 320 File

USDC SDNY
DOCUMENT
ELECTRONICALLY FILED
DOC #:
DATE FILED: 10/24/2018

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:

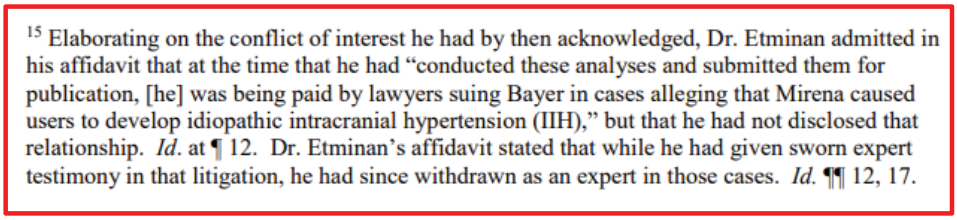
MIRENA IUS LEVONORGESTREL-RELATED PRODUCTS LIABILITY LITIGATION (NO. II)

This Document Relates to All Actions

17-MD-2767 (PAE)
17-MC-2767 (PAE)

OPINION & ORDER

PAUL A. ENGELMAYER, District Judge:



[15] Elaborating on the conflict of interest he had by then acknowledged, Dr. Etminan admitted in his affidavit that at the time that he had "conducted these analyses and submitted them for publication, [he] was being paid by lawyers suing Bayer in cases alleging that Mirena caused users to develop idiopathic intracranial hypertension (IIH)," but that he had not disclosed that relationship. *Id.* at ¶ 12. Dr. Etminan's affidavit stated that while he had given sworn expert testimony in that litigation, he had since withdrawn as an expert in those cases. *Id.* ¶¶ 12, 17.

- Epidemiologist failed in publication to disclose role as plaintiff expert witness in multi-district class action
- SDNY dismissed epidemiologist's credibility in *Daubert* ruling, citing unreliable methodology, retraction, **and undisclosed financial conflict**

Source: *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig., 2018 U.S. Dist. LEXIS 182420, __ F. Supp. 3d __, 2018 WL 5276431*

Conflicts of Interest Policies Under the NY Not-for-Profit Corporation Law

Conflicts of Interest of Board Members

- The NY ***Not-for-Profit Corporation Law*** (NPCL) requires directors to make disclosures about potential conflicts of interest at the beginning of their service, annually, and when issues come before the board
- Conflicted directors must abstain from participating in board deliberations and decisions on those issues

Tension Between Banning All Conflicts vs. Permitting Path to Manage Conflicts

- "An effective COI policy ensures that potential COIs do not disqualify board members from serving non-profit corporations, but rather enables the non-profit to benefit from having skilled and connected board members"

Source: *NY State Charities Bureau*

NY Non-Profit Conflict Policy Requirements

1. A definition of circumstances that constitute a conflict (N-PCL § 715-a(b)(1)).

2. Procedures for disclosing conflict to the board or committee (N-PCL § 715-a(b)(2)).

3. Requirement that conflicted individual not vote or be present at board or committee deliberations on the matter giving rise to such conflict (N-PCL § 715-a(b)(3)).

4. Prohibition of any attempt by the person with the conflict to influence improperly the deliberations or voting on the matter (N-PCL § 715-a(b)(4)).

5. Requirement that existence and resolution of a conflict be documented, in the minutes of meetings where conflict was addressed (N-PCL § 715-a(b)(5)).

6. Procedures for disclosing, addressing, and documenting related party transactions pursuant to N-PCL § 715. Related party transactions include any transaction, agreement, or other arrangement in which a related party has a direct or indirect financial interest with the nonprofit or an affiliate (N-PCL § 715-a(b)(6)).

Source: *NY State Charities Bureau*

Attorney Ethics in Advising on Research Conflict of Interest

Some Challenges:

- ☐ Organization as client
- ☐ C-suite executives, senior physicians and scientists have substantial political muscle within organizations and within governing boards, and interests at issue may be personal to them
- ☐ Same for tech transfer directors and officers, and few written guidelines for their deal-making
- ☐ Lawyers can be blamed for saying “no” or advising caution
- ☐ “Institutional conflict” remains undefined and attorney may face push-back when recommending divestment or avoidance of potential conflicts

NEW YORK STATE UNIFIED COURT SYSTEM

PART 1200

RULES OF
PROFESSIONAL CONDUCT

NY Rules of Professional Conduct
1.13 Organization as Client

The Entity as the Client

- ☐ An organizational client is a legal entity, but it cannot act except through its officers, directors, employees, members, shareholders and other constituents

- ☐ If the organization's interests differ from those of its constituents, the lawyer should advise that:
  - (i) a conflict or potential conflict of interest exists
  - (ii) the lawyer doesn't represent the constituent (unless concurrent rep approved)
  - (iii) the constituent may wish to obtain independent representation
  - (iv) any attorney-client privilege that applies to discussions belongs to the organization

Source: *NY Rules of Professional Conduct with commentary as amended through January 1, 2017, Rule 1.13*

NY Rules of Professional Conduct 1.13 Organization as Client

Concurrent Representation

- ☐ A lawyer for an organization may also represent a principal officer, subject to the provisions of Rule 1.7 with the corporation's consent

"Best Interests" of Hospital

- ☐ If a person associated with the organization violates an obligation to the organization or a law that reasonably might be imputed to the organization, and is likely to result in substantial injury to the organization, **"the lawyer shall proceed as is reasonably necessary in the best interest of the organization"**

- ☐ Measures may include asking for reconsideration of the matter and referring the matter to a higher authority in the organization

Source: *NY Rules of Professional Conduct with commentary as amended through January 1, 2017, Rule 1.13*

NY Rules of Professional Conduct
1.7 Conflict of Interest: Current Clients

- "The professional judgment of a lawyer asked to represent several individuals operating a joint venture is likely to be adversely affected to the extent that the lawyer is unable to recommend or advocate all possible positions that each client might take because of the lawyer's duty of loyalty to the others."

A lawyer may provide concurrent representation if:

(1) the lawyer reasonably believes that the lawyer will be able to provide competent and diligent representation to each affected client;
(2) the representation is not prohibited by law;
(3) the representation does not involve the assertion of a claim by one client against another client represented by the lawyer in the same litigation or other proceeding before a tribunal; and
(4) each affected client gives informed consent, **confirmed in writing**.

Source: *NY Rules of Professional Conduct with commentary as amended through January 1, 2017, Rule 1.7*

NY Rules of Professional Conduct
1.7 Conflicts in Transactional Practice

Non-litigation Conflicts

☐ Relevant factors in determining whether there is a significant risk that the lawyer's professional judgment will be adversely affected include: (i) the importance of the matter to each client, (ii) the duration and intimacy of the lawyer's relationship with the client or clients involved, (iii) the functions being performed by the lawyer, (iv) the likelihood that significant disagreements will arise, (v) the likelihood that negotiations will be contentious, (vi) the likelihood that the matter will result in litigation, and (vii) the likelihood that the client will suffer prejudice from the conflict. The issue is often one of proximity (how close the situation is to open conflict) and degree (how serious the conflict will be if it does erupt).

Source: *NY Rules of Professional Conduct with commentary as amended through January 1, 2017, Rule 1.7*

NY Rules of Professional Conduct 1.6 Confidentiality of Information

Attorneys May Seek Independent Advice

- "A lawyer's confidentiality obligations do not preclude a lawyer from securing confidential legal advice about compliance with these Rules and other law by the lawyer, another lawyer in the lawyer's firm, or the law firm"

Source: *NY Rules of Professional Conduct with commentary as amended through January 1, 2017, Rule 1.6*

NY Rules of Professional Conduct
1.6 Confidentiality of Information

A lawyer may reveal or use confidential informati the extent that the lawyer reasonably believes necess

(1) to prevent ably certain ly ha

(2) to **prevent t**

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law by the law or the

(5) (i) loye associates against an stablish or collect a fee; or

(6) when perm equir der these Rules or to comply with other law or court order.

Rules for breaching attorney-client privilege or 'noisy withdrawal' require prevention of crime or fraud-- not merely prevention of reputational harm to institution

Source: *NY Rules of Professional Conflict, Rule 1.6*

Questions?