

When things go wrong...

Outcomes and Consequences

Pat Ward
Director, Regulatory Affairs

The institution has made its necessary reports

- OHRP
- FDA
- Sponsor
- Accreditor
- Other

Now what?

Agency and other follow-up and fall-out...

- CAPA implementation
- Letters of explanation and apology
- Site visit or inspection
- Additional response
- Legal action
- Media attention
- Information requests
- Distraction
- Rejected/retracted publications
- Delayed/returned funding
- Fines
- Research restrictions and sanctions
- Reputational harm
- Criminal prosecution

CAPA implementation

The institutional self-report likely includes a corrective and preventive action (CAPA) plan

Construct it carefully

- Must be responsive to the problem(s) cited
- Must satisfy (but don't over-do)
- Must do what promised (and document it)
- Must be effective (how will you check?)
 - Or get permission to try another way

CAPA Plan – Typical Elements:

Corrective

- Fix problem if possible (make it right)
 - Correct error
 - Re-consent
 - Notifications, reports

Preventive

- Change going forward
 - Personnel
 - Procedures
- New “tools” to help do better
 - SOPs
 - Checklists
- Training (including content and logs)
 - On existing rules
 - On new changes and tools
- PDCA / Audit

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Special CAPA Plan Element

Letter of explanation and apology to research subjects

Who weighs in

- PI (and Department, School)
- IRB
- General Counsel
- Risk Management / Clinical Safety
- UM Office of Research
- Sponsor

What it says

- This is what happened
- Here's how it might impact you
- It was my responsibility
- I apologize
- (Here's how it can be made up to you)

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Federal Inspection Likely

- FDA or other agency (OHRP, etc.) inspects
- No findings
 - Unlikely, but has happened
 - Make sure to follow through on CAPA promises
- Findings
 - FDA Form 483, for example
 - Respond within 15 business days
 - More robust than self-report
 - Enhanced CAPA

FDA determinations after response

NAI – No Action Indicated

- No 483 or findings not actionable

VAI – Voluntary Action Indicated

- Self-report and CAPA acceptable and sufficient
(but do it!)
- Usually no further response necessary

OAI – Official Action Indicated

- Usually requires additional response
 - Earlier response not adequate
 - Deficiencies serious or pervasive

Official Action Indicated (OAI)

Untitled letter

- Requests further action or response
- Serious but not unmanageable

Warning letter

- More serious
 - Repeated or deliberate violations
- PI may receive for conduct of study team
 - Failing to properly supervise
- Posted on FDA public website
- May attract media and sponsor attention
- Requires serious action and response
- “Shot across the bow” for possible FDA sanctions

The path you don't want to head down...

NIDPOE

- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain
- Receive if response to Warning Letter is not adequate
- Posted on FDA website
- May attract media and sponsor attention
- First step toward career threatening sanctions
- Time to get legal advice/representation

The path you don't want to head down...

NOOH

- Notice of Opportunity for Hearing
- Posted on FDA website
- May attract media and sponsor attention
- Legal representation strongly advised

The path you don't want to head down...

Disqualification

- Can no longer serve as clinical investigator on FDA-regulated trials
- Action taken when testimony at hearing is not adequate
- Name included on website List of Disqualified Investigators
- Likely to attract media attention
- Likely to be seen and considered by current and future potential collaborators, sponsors, employers

What about OHRP?

FDA

- Focus is on the individual (clinical investigator)
- Can get to institution through IRB

OHRP

- Focus is on the institution (assurance)
- If pull assurance, effectively stops federal funding flow

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Liability in Clinical Trials Research

Kenneth A. De Ville, PhD, JD

Denise Brigham, BSN, RN, MPH

Lawsuits involving human research are not new, but they are on the rise.

Research participants may sue the study sponsor, study investigator, medical school, hospital, research center, group practice,..., as well as the institutional review board (IRB) that reviewed and approved the study...[but] **likely the physician-investigators who actually conduct the study.**

...suits against physician-researchers have asserted claims under...some theory of **negligence**...

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NYT on NYU...

Drug Trial Scandal at N.Y.U.? What We Know

By Neuroskeptic | June 29, 2016 1:54 am

The ***New York Times*** breaks the story of an ostensibly serious case of misconduct at New York University (NYU):

New York University's medical school has quietly shut down eight studies at its prominent psychiatric research center and parted ways with a top researcher after discovering a series of violations in a study of an experimental, mind-altering drug.

A subsequent federal investigation found lax oversight of study participants, most of whom had serious mental issues. The Food and Drug Administration investigators also found that records had been falsified and researchers had failed to keep accurate case histories...

The violations *"jeopardize subject safety and welfare, and raise concerns about the validity and integrity of the data collected at your site,"* the F.D.A. said in a letter, obtained by The Times, to Dr. Alexander Neumeister, the studies' lead investigator.

What to do if a reporter contacts you...

Call UMHS Communications

- 764-2220 (936-4000 after hours)
- Time is critical
 - reporters have tight deadlines
 - news spreads fast on social media
- Communications can help you:
 - Decide whether or not to give an interview
 - You don't have to, Communications can handle for you
 - Anticipate questions
 - Prepare key messages

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[\(https://foia.vpcomm.umich.edu/\)](https://foia.vpcomm.umich.edu/)

MICHIGAN'S FREEDOM OF INFORMATION ACT

Summary

Section 1 of the Michigan Freedom of Information Act ("FOIA" or "the statute") provides, "It is the public policy of this state that all persons, except those persons incarcerated in state or local correctional facilities, are entitled to full and complete information regarding the affairs of government and the official acts of those who represent them as public officials and public employees, consistent with this act. The people shall be informed so that they may fully participate in the democratic process." To that end, all people, excluding prisoners, are allowed to file FOIA requests with a Public Body. A requester must simply file a request in writing with the University's FOIA Office, and the University will begin processing his or her request.



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Fraud and misconduct in clinical research: A concern

Ashwaria Gupta

WHAT COULD BE THE IMPACT OF FRAUD?

The impact on affected individuals and the research community can be profound. Such incidents result in huge cost to the sponsor in terms of additional resource for investigating fraud and cost of possibly repeating those aspects of research, which were fraudulent. It can also leads to disciplinary action for researchers. Such a researcher may not be allowed to be a part of any advisory committee or peer review board. **Any article published by such a researcher might be re-reviewed and retracted if required.** Fraudulent clinical research also affects the validity of data and impacts the core of good clinical practice adversely, i.e., rights, safety and well-being of research participants. On a broader scale of impact on health-care, it can lead to wrong or ineffective or harmful molecules being brought in the market.

Noncompliance — **IRB Approval**

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Noncompliance = Unallowable Costs

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FDA Ups Monetary Penalties for Regulatory Noncompliance

Alexander Gaffney, RAC

The US Food and Drug Administration (FDA) has announced

(https://www.federalregister.gov/articles/2014/06/06/2014-13165/maximum-civil-money-penalty-amounts-civil-moneypenalty-complaints?utm_campaign=pi+subscription+mailing+list&utm_medium=email&utm_source=federalregister.gov)

it will implement without change a regulation proposed earlier this year that is set to increase the **monetary penalties** for persons and companies found guilty of noncompliance with federal drug and device law.

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- Institutional
 - Including dismissal
- IRB
- Agency



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Remember the NYU researcher?



Alexander Neumeister
2007 photo
From <http://www.medicineatnyu.org/>

And who is Alexander Neumeister? He is, or was, a prolific and successful researcher. Neumeister has published **155 scientific papers over a 20 year career**, many of which have been **highly cited**. Neumeister's early research was focussed on depression and especially on the role of serotonin in that disorder. His interest in the cannabinoid system appears to be relatively recent; his first cannabinoid paper **is from 2011**.

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Most criminal prosecutions of clinical trial researchers are for fraud, but...



**But wait,
There's hope!**

But wait, there's hope!

- Know your stuff
 - protocol, approvals, etc.
- Hire well
 - investigators and staff
- Train well
- Supervise well
 - careful and documented delegation
 - communicate, be brave
 - share problems and encourage others to do same
 - resolve confusion and difficulties

No problem ever got smaller by ignoring it!

But wait, there's hope!

- Choose well
 - Sound risk-benefit
 - Logistically feasible
 - Doable study, test drive it
- Commit to the protocol
 - Either follow the protocol or...
 - Follow established process for changes or departures
 - Safety is paramount!
- Assess and Document
 - Clear, complete, timely, thoughtful, sound judgment
 - Don't just go through the motions
 - Don't fall behind

But wait, there's hope!

- Control and Accountability
 - Activities, materials
- QC/QA
 - Spot-check, fresh eyes,
 - But double-check advice
- Report!
 - It takes a village

GOOD
Things
That Happened
TODAY ooo

