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# Supplementing Traditional Research Compliance Monitoring and Auditing with Anticipatory Surveillance

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## Disclosures

*Robert Bienkowski* I have no personal or professional relationship(s) relevant to this presentation

*Lynn Smith* I have no personal or professional relationship(s) relevant to this presentation

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## Generic Policy Statement about Review & Approval of Research with Human Subjects

All research involving the use of human subjects conducted by university faculty, staff or students, or sponsored in part or in whole by university, must be reviewed and approved prior to the start of the project and then conducted in full compliance with IRB policies and procedures.

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## The Provost's Concern

How do I know that all research involving human subjects at my university has been reviewed and approved by the IRB?

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## Rationale for this Session

- Undetected research noncompliance presents risks to subjects, institutions, researchers, and entire fields of research
- Formal systems of monitoring and auditing have inherent blind spots to some types of research noncompliance
- Anticipatory surveillance is a proactive, predictive compliance activity that assists in the early detection of potential noncompliance and mitigation of noncompliance before it becomes serious

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## Part 1. The Story

This is a story about medical research to develop a treatment for herpes that went terribly wrong.

The story has been described in detail in the popular press and healthcare publications.

We will not name the investigator or the institution – although they can be identified with a simple internet search.

This session will seek to answer the questions ...

*Could this happen at my institution on my watch?  
How can I prevent it?*

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## Herpes

- Sexually transmitted disease caused by a virus HSV 1 or HSV 2.
- One out of every 6 persons ages 14 – 49 has genital herpes
- Characterized by sores in genital area and frequent outbreaks
- Can be treated but not cured

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## Chronology

- 2007 Dr H was hired at the medical school of a middle-size university in the Midwest. He was a microbiologist focused on developing a vaccine to treat herpes. He was not a physician.
- 2010 Dr H applied for patent for a vaccine
- 2011 Dr H diagnosed with sinonasal undifferentiated carcinoma (5-year survival)
- 2012 Dr H injected himself and his family members with the vaccine. Later, he told subjects “If we didn't have a problem, you shouldn't have a problem”
- 2012 Dr H formed a company

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- 2013 Dr H injected ~ 8 persons with experimental vaccine at motels near the university  
No indication of IRB approval or IND application; no indication of where vaccine was produced
- 2014 US Patent issued; lists Dr H and someone else  
Assigned to {University} and another university
- 2015 {University} licensed patent to Dr H's company  
{University} COI committee reviewed Dr H's work at {University} and at company
- 2016 {University} administrators attended Dr H's presentation of vaccine at a technology exposition sponsored by {University}.  
Dr H told medial school dean that the presentation was about his work at the company

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- 2016 Dr H injected experimental vaccine to subjects in St Kitts
- 2017 Government of St Kitts stated it was never informed of the experiments
- 6/17 Dr H dies
- 7/17 Concerns raised about Dr H's research with {University} leadership
- 8/17 {University} IRB began investigating whether there were any areas of noncompliance  
Internal review found that "serious noncompliance with regulatory requirements and institutional policies and procedures occurred"
- 9/17 OHRP requests report about the "clinical trial"

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## Statement by Company - 2015

The co-founder did not meet Dr H until 2014, and {Company} was not formed until February 2015. As such, neither {Co-Founder} nor {Company} had any involvement with Dr H research prior to those times.

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## Statements by University Director of PR

“... the IRB and the university are reviewing whether the research and any trial should have been brought to the IRB by the primary investigator, since his research was conducted by a private company, {Company} — not {University}.” {University} is reviewing its procedures and communication with principal investigators concerning any research they perform independently from their roles as faculty members.

The medical IRB’s policies state that it is responsible for reviewing proposed research that includes humans as subjects when the study is conducted by a member of the research institution’s faculty, staff, residents, and students.

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{University} issued a statement in late August, acknowledging that {Company} licensed intellectual property from {University} through university's office of technology transfer. Within that license agreement, both {Company} and {University} are responsible for upholding all applicable laws and regulations associated with the license.

The statement also says that {University} is not responsible for trials and research conducted by independent companies.

"I haven't had any communication with {Company}," {Director PR} says.

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"I haven't had any communication with {Company}," {Director PR} says.

## Letter From OHRP - Sept 2017

As you are probably aware, according to {University Spokesperson}, {University} officials were unaware of this trial until it was done and she asserts that the trial was not conducted by Dr H as part of his faculty appointment at {University}. (Spokesperson) is quoted as stating "The research in question was run by Dr H in his role as the chief science officer of {Company}, an independent company, not as a faculty member of {University}."

According to OHRP's records, {University} applies HHS regulations to all of its research, regardless of funding. As such OHRP is requesting a report of {University's} involvement in the trial, if any. Please provide OHRP with the results of {University's} evaluation of its jurisdiction over this research, along with documentation to support your determination no later than October 6, 2017.

For guidance on whether your institution would be considered engaged in this research, please refer to OHRP's 2008 ... Guidance Document found at ...

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## University Response – Oct 2017

{University} first became aware that {Company} had conducted the Trial on October 13, 2016. {University} had not been involved in the development, funding, operation or oversight of the Trial. {University} employees are permitted to, and regularly do, perform work outside of their employment with {University}. Dr H's work with {Company} was performed outside of the scope of his employment. It was {University}'s understanding that {Company} had been responsible for the management and oversight of the Trial, including work with a local physician in St. Kitts to monitor participants and obtain the necessary governmental approvals.

Because {University} was not involved in the Trial in any way and viewed it as the business operations of a private company, {University} did not feel that any discussion with Dr H about the Trial was warranted. To date, there also has been no indication that {Co-Founder} or Dr H viewed the activities of {Company} to be the activities of {University}.

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## Aftermath

- Various scientific journals declined to publish papers submitted by Dr H. Reviews were extremely critical, dismissive, and skeptical. Some expressed alarm about ethical issues.
- Responses of persons injected with vaccine ranged from claims of "functional cure" to significant mitigation of symptoms to exacerbations. There were many adverse events.
- 3/18 - Three participants have filed suit alleging research violated US and international laws aimed at protecting human subjects. Represented by Alan Milstein.

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## Discussion Points

- Was Dr H a *rogue* investigator?
- Was the university's claim that Dr H was not an *agent* credible?
- Was the university *engaged* in this research?
- Have you seen anything like this at your institution?

## References

US Patent 8,802,109. *Herpes simplex virus mutant* ICPO. August 12, 2014

*Quotations were drawn from several sources:*

Desperate quest for Herpes Cure Launched 'Rogue' Trial

Marisa Taylor, Kaiser Health News Oct 19, 2017

Investigation: {redacted} scientist's herpes vaccine violated rules

Dean Olsen, The State Journal, Nov 8, 2017

'Unethical' herpes trial could cost university millions in research funding

Rachel Pells, Times Higher Education, Dec 5, 2017

FOIA Request, Dean Olsen, Oct 27, 2017

Participants In Rogue Herpes Vaccine Research Take Legal Action

Marisa Taylor, WaPo & Kaiser Health News March 13, 2018

## Part 2. Research Administration

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## Believe it or not ...

*These things happen frequently!*

- An investigator proposed sending the research nurse to take PKs in a hotel room so that subjects wouldn't have to stay in the hospital overnight. The university IRB approved the protocol that clearly described the administration of an investigational drug in a hotel room.
- An investigator wanted to take what was left of an experimental drug in the tubing that used to administer it to human subjects. His intention was to study its effects on rodents in his lab. A vigilant nurse brought it to the attention of the Research Unit Manager and it was stopped.
- An investigator proposed meeting parents and subject children at a Safeway parking lot after hours to draw blood on children because it was too inconvenient for the parents to come into the clinic during the day.

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## Rogue is *not* a compliance term

Urban Dictionary rebellious, loner who follows their own rules

Cambridge Dictionary person, organization, or country that does not behave in the usual or acceptable way

## What is a "rogue" investigator?

An investigator who, while acting as an agent of the institution and, therefore, engaging the institution in the research, conducts unapproved research involving human or animal subjects.

- What is an agent?
- What does it mean to be engaged?

## Agency (not defined in regs)

The relationship of a person (called the agent) who acts on behalf of another person, company, or government, known as the principal.

The basic rule is that the principal becomes responsible for the acts of the agent, and the agent's acts are like those of the principal.

Law.com

## Engaged (OHRP definition)

In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.

<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html>

## In other words...

An institution is engaged in research when its agents conduct research

## Where is the Breakdown?

There are opportunities to catch problems *within, between, and among* various Research Administration offices:

- Tech transfer
- Licensing
- Contracts
- Research Review Boards
- Research Compliance
- Labs and Pharmacy

## Components of Oversight

### Contracts

- Who is supporting this research?
- Is it the institution?
- Is it a private company?
- Who is contractually responsible for the conduct of the research?

## AAHRPP Standard I-8

The organization works with public, industry, and private sponsors to apply requirements of the Human Research Protection Program to all participants

## Additional clauses

The contract can require licensee to:

- Submit periodic reports
- Conduct human subjects research according to 45 CFR 46 or 21 CFR 50 and 56

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## Components of Oversight

Research Review Boards

- Is there a formal Scientific Review?
- IRB
  - Does the protocol adequately address who, what, when, where and why?
- Ancillary committees?
  - Radiation Safety?
  - Biosafety?
  - Other Committees or Offices?

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## Components of Oversight

### Research Compliance

- Is anyone monitoring ongoing research (especially investigator-initiated research)?
  - When the investigator is the IND/IDE holder, they are also the sponsor – so they must fulfill all regulatory requirements of the investigator and of the sponsor!
  - If the institution is able to support this, consider contracting with a CRO to manage the trial

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## Components of Oversight

### Labs and Pharmacy

- How did the investigational product get from the lab or the pharmacy to the location (off-shore or in a hotel room) without someone along the way knowing?
  - What were the institutional policies and procedures related to manufacturing, control, transfer and administration of an experimental drug?

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## Components of Oversight

### Other Entities

Would you bring in any other entities at your institution, either routinely or ad hoc?

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## How do you Manage at Your Institution?

- What processes do you have in place to address incidents?
- Do you proactively look for gaps in compliance?
- Do you use social media as a tool?
- What types of issues have you dealt with?

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## Part 3. Monitoring & Surveillance

Monitoring: observing and checking the progress or quality of an activity over a period of time; keeping something under systematic review.

Surveillance: observing behavior or activities for the purpose of influencing, managing, directing, or protecting people or institutions.

*The concepts are related but distinguishable.*

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***Expectation of Non-Compliance***

***Knowledge of Activity***

**Monitoring**

**Surveillance**

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# Surveillance for Unapproved Research

## Not a New Concept

### Four Concepts of Monitoring (Heath, 1979)

1. Continuing review
2. Review of the consent process
3. Review for adherence to protocol
4. Review to identify unapproved activities

## What Should You Surveil\*?

- Social Media
  - Institutional pages: “Public” pages with public posts
  - Personal pages: Public posts from private pages
- On-line traditional media sources
  - Internal news (University publications)
  - Local news
  - National

\*The verb surveil, originally a back formation of surveillance, was long considered nonstandard, and even now is still so new to the language that some dictionaries don't include it. (*grammarist*)

## What Should You Surveil?

- “Public” pages are easy to follow and set up “alerts” to be sent to you by e-mail, this allows for continuous surveillance with minimal effort.
- Private pages that make relevant public posts about your institution: periodic searches with keywords (e.g. “research” “your institution”)
- Other ideas: Google alerts (search term alerts)

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## Getting Started

- What do we need to monitor/surveil?
- How often?
- What needs to be documented?
- Who needs to be involved and who else can be?
- Write it down (SOP).
- Keep it simple!

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## How Often?

- Tailor to your institutional needs and resources.
- Continuous “alerts” require little or no investment of time.
- Periodic formal searches:
  - About an hour, once a week.
  - Searches of social media, search engines and publications.
  - Your institutional communications department or libraries may be of assistance in this area.

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## What to Document

- Logging/Tracking all positive matches for your search terms is likely to be overwhelming!
- If you want to establish metrics, recording the number of positive matches may be sufficient
- Log details of any match that requires follow up:
  - The story is about regulated research
  - Something in the story doesn't add up or simply needs confirmation

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## When to Document in Detail

- The story is about research at your institution and requires confirmation of approval and/or follow up with the PI (monitor/audit).
- The activity, as described, clearly stands out as something that would require oversight committee approval but no protocol exists (surveillance).

## What Details to Document

- The source
- Date discovered
- PI and protocol (if known), or oversight area
- A summary of the concern
- The date and a summary of any relevant findings
- If the finding indicates potential non-compliance

## What Triggers an Investigation

- Finding that no protocol exists
- The protocol involved in the research mentioned in the story has expired but appears to describe ongoing research
- Details of the story differ from the approved protocol
- The PI can't explain a discrepancy
- The Committee or Chair request initiation of an investigation

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## Metrics

Like many institutions, we are resource (personnel) limited, so we don't track all matches to CMU research during continuous surveillance except:

- Periodically to assess volume and generate metrics (select periods of 4-6 weeks)
- The number of matches that involve regulated research
- The number of matches that required follow up
- The number of matches/follow-ups that result in findings of non-compliance

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## Metrics: 2017-2018

- More than 60% of matches resulted in simple verification of an approved protocol or that the research was exempt (e.g. the project was NHSR)
  - About 15% resulted in consultation with PI
  - This has been a valuable complement to Post Approval Monitoring
- About 15% resulted in findings of non-compliance (mostly minor)

## Pro-Active Prevention of Non-Compliance

- Most non-compliance is minor and involved unapproved alteration of recruitment or consent materials.
- Only one finding of serious/continuing non-compliance.
- Follow-up meetings with 45 PIs in 2017 and 2018.
  - 8 resulted in submission of an amendment, a new protocol or change in NHSR research plan.
  - Without these submissions prior to initiation of planned research, non-compliance would likely have occurred.

## Heightened Awareness University-Wide

- University Communications
- University Libraries
- Departmental offices responsible for social media accounts (Facebook, Twitter, Instagram, YouTube)
- Oversight committee members
- ORC/IRB/IACUC staff
- Investigators

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## Development of Guidance

- Guidance on Advertisement and Recruiting
- Definitions and guidance on what “enrollment” and “pre-screening” mean and how they differ

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## Impact of Surveillance: 2018-2019

- More than 70% of matches resulted in simple verification of an approved protocol or that the research was exempt (e.g. the project was NHR), compared to ~60% in prior years.
- 8% of matches resulted in PI consultation
- Some continued monitoring of ongoing activities, but non-compliance findings have decreased dramatically.
- Investigators are paying attention!

## Response to Provost's Concern About Unapproved Research

We check this on a regular basis.

We haven't found any rogues ... *yet*.

We've found some "leakage," *ie*, minor noncompliance.

We're talking to the investigators.

## Concluding Remarks

Two elements of an efficient compliance program are *monitoring* approved research in real time and *auditing* records of what was done.

Our examination of recent stories in media/social media – and our own experience - suggests that a third, distinct, element, *anticipatory surveillance*, is useful in identifying activities that can, if not checked, lead to serious noncompliance.

# Questions?

Thank You