What is regulated research?
and
Why do we care?

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The Journey

- Introduction
- Archetypes
- Ethical Framework of Regulated Research vs Clinical Operations
- The Fine, Regulatory Line Between Research and Clinical Operations
- The KPHI Process for Making Research/Not Research Determinations
- Questions and Answers

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A Psychology Experiment:

Using the index cards on your table, record the first 2 – 3 adjectives that come to mind as you see the following words:

DOCTOR

SCIENTIST

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ar·che·type /ärkəˌtīp/

A typical character, an action, or a situation that represents universal patterns of human nature.

DOCTOR

SCIENTIST

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Examining the evidence……

Entertainment as a window into public perception of the doctor versus the scientist

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The Strange Case of Dr Jekyll and Mr Hyde (1886)

- **Dr Jekyll:** a kind English doctor in Victorian London – seemingly prosperous and known for his decency and charitable works …

Develops a drug (aka research/science)
transforming him into…

- **Mr Hyde:** has no conscience, no restrictions, no boundaries; he is free to do what he pleases.

- **Motivation / Intention** = To expand capabilities beyond his human limitations

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Jurassic Park (1993)

- **John Hammond:** "I don't think you're giving us our due credit. Our scientists have done things which nobody's ever done before..."
- **Dr. Ian Malcolm:** "Yeah, yeah, but your scientists were so preoccupied with whether or not they could that they didn't stop to think if they should."

- **Motivation / Intention** = Science for the sake of science

Maze Runner: The Death Cure (2018)

- **Thomas:** "How many kids do they have to round up, torture, kill? When the he[ck] does it stop?
- **Teresa:** "It stops when we find a cure."
- **Teresa:** "The world is dying. If we find a cure that's the only way all of this was worth it."

- **Motivation / Intention** = To save the world, the ends justify the means
  - **Ethic** = the needs of the many outweigh the needs of the few

Archetypes = Real Life?

OHRP* Letter to U of Alabama at Birmingham June 4, 2013

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

Research Project: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Principal Investigator:

Dr. Waldemar A. Carlo

***Department of Health and Human Services, Office of Human Research Protections**

Excerpt from the letter:

Ultimately, the issues in this case come down to a **fundamental difference between the obligations of clinicians and those of researchers**. Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation: Our society relaxes that requirement because of the need to conduct research, the results of which are important to us all.

Posted on the OHRP website

What if the doctor is the scientist/researcher?

The Exact Same Activity Can Be Regulated Differently Depending on the Purpose

Public Health Surveillance
- Protect the public
- ➢ State Regulation

Clinical Operations
- Care for individuals
- ➢ Accreditation & Professional Standards

Research
- Create new knowledge
- Market a drug or device
- ➢ Federal Regulation

Regulation reflects the ethical framework

- Public Health Surveillance
  - Protect the public
  - The needs of the many outweigh the needs of the few
- Clinical Operations
  - Care for the individual patient
  - Hippocratic Oath → World Medical Association, Declaration of Geneva (updated in 2017)

  "The health and well-being of my patient will be my first consideration"
- Research
  - The Belmont Report

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Ethical Framework for US Research Regulation

Europe

- Nuremberg Code (1947) American judges; Nazi doctors
- Declaration of Helsinki (1964) World Medical Association

US Public Health Service

"Tuskegee Study of Untreated Syphilis in the Negro Male"

- Treated for "bad blood" (1932)
- Free meals, medical exams and burial insurance
- 1947 Penicillin becomes Standard of Care
- Study stopped in 1972

National Research Act (1974)

- National Commission for the Protection of Human Subjects of Research → **Belmont Report**
- The **Common Rule** for the protection of human subjects of research

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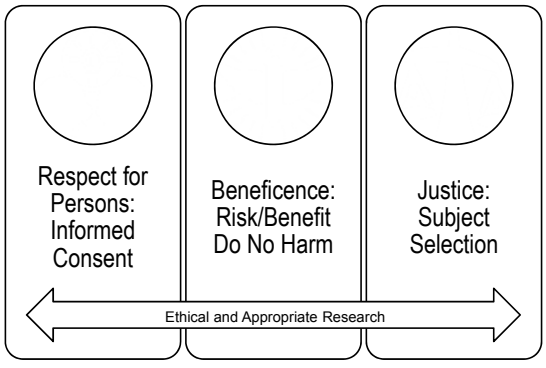

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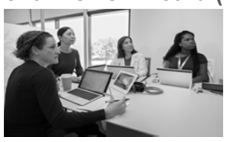
Common Rule: Institutional Review Board (IRB)



- Ethical review board
- IRB is composed of
  - Scientists and non-scientists
  - affiliated and non-affiliated
- Responsible for the protection of human subjects of research by ensuring that (regulated) research protocols are consistent with the ethical standards established by the Belmont report and are compliant with regulatory and statutory requirements
- The IRB has the authority to approve, disapprove, or require modification to a research protocol in order to secure approval
- If the IRB disapproves a research protocol, the institution can not approve the protocol.

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Applying this interaction between intention, ethical framework and regulation to <u>research</u>

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re·search /rē¸sərCH/

Dictionary Definition

- the systematic investigation into and study of materials and sources in order to establish facts and reach new conclusions

Regulatory Definition (Common Rule, HIPAA, FDA*)

- a systematic investigation…**designed** to develop or contribute to generalizable knowledge
- 45 CFR 46.102
- 45 CFR 164.502
- 21 CFR 56.102 (Clinical investigation includes research)

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de·sign /dəˈzīn/

- purpose, planning, or intention that exists or is thought to exist behind an action, fact, or material object

How do you monitor compliance when the observable actions can be regulated differently based on the purpose or intention?

How do you tell the difference between research and regulated research?

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Why do we care?

- Regulatory Compliance – recognizing it is the first step
- Protecting our doctors and staff – when requirements change based on intentions, it is difficult to recognize when you crossed the line (assuming awareness that there is a line to cross…)
- Therapeutic misconception – tendency to not understand that in the research process the "health and well-being of the patient" is not the first consideration.
  - An issue for patients and also for physicians
- Avoid "regulatory creep"

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Institutional process for making

regulated research vs

not research (e.g., clinical operations)

determinations

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Federal Guidance (OHRP FAQ)

The regulations do not specify who at an institution may determine that research is exempt under 45 CFR 46.101(b). However, OHRP recommends that, because of the potential for conflict of interest, investigators not be given the authority to make an independent determination that human subjects research is exempt.

The Traditional Approach

- Submit it to the IRB, and allow the IRB to decide

The Problem with the Traditional Approach

- Because the IRB submission process presumes the requestor is doing research, the submission is molded into "pseudo-research"
- The IRB tends to default to assuming it is research
- The process is long and tedious
- It is illogical to go through a long, tedious process for a determination that you don't need to go through said process.

Key Considerations

- Process must have quick turn-around time
- Process must encourage submission of the least amount of information needed to reach an informed decision
- Process should provide an incentive to encourage doctors and staff to want to submit
- Process should provide leadership with tangible benefit
- Additional thoughts:
  - IRB/compliance staff have subject matter expertise, but may have a tendency to be overly conservative
  - Regulation allows combining "not research" and "exempt human subjects research" determinations into a single process

The "Research Determination Officials" Team

- A 3 person team empowered with institutional authority to determine whether research activities are regulated research and/or exempt from IRB review.
  - A research operational manager
  - A senior level Medical Director
  - A research compliance professional or IRB Administrator
    - Also empowered to determine that certain activities are exempt from IRB review
- Goal to operate using consensus decision-making

Addressing Key Considerations

- The RDO submission process is easy and fast
  - Form is 1 page blank → 2 – 3 pages when completed
  - Turn-around time is approximately 5 business days
- The tangible benefit is a written determination that the research doesn't require IRB review (for journal editors, facility leadership, etc.)
- The incentive for leadership is improved visibility into what is happening in the patient space
- Alerting staff about the process increases the overall awareness of the difference between research and regulated research

Questions?