

Managing Preclinical Risk to Protect Data Integrity, Animal Welfare, and Human Subject Safety

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HCCA Research Compliance

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Alison Powell LATG is involved in auditing and reviewing preclinical and laboratory based research throughout Northwell Health for quality assurance and improvement, and providing education to the investigative community. Alison graduated from Manhattan College, and has worked at Weill Cornell Medical College/Memorial Sloan-Kettering Cancer Center's Research Animal Resource Center program, as an animal husbandry technician.



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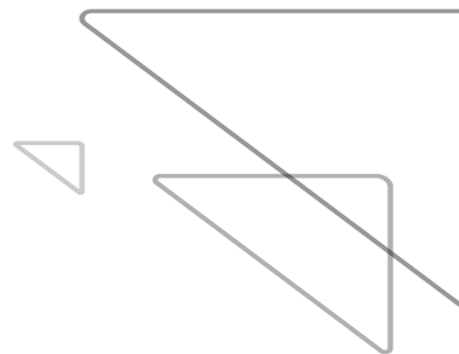
Today's Objectives

- Understand the development of biomedical technology from the bench to the bedside
- Understand how compliance oversight, and risk management can help lead to quality, reproducible data, increased animal welfare, and safe foundational knowledge for early phase clinical trials
- Review and discuss relevant cases that exemplify researcher and subject risk, and how they affect bench research, animal studies, and early phase clinical trials



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Drug and Device Development



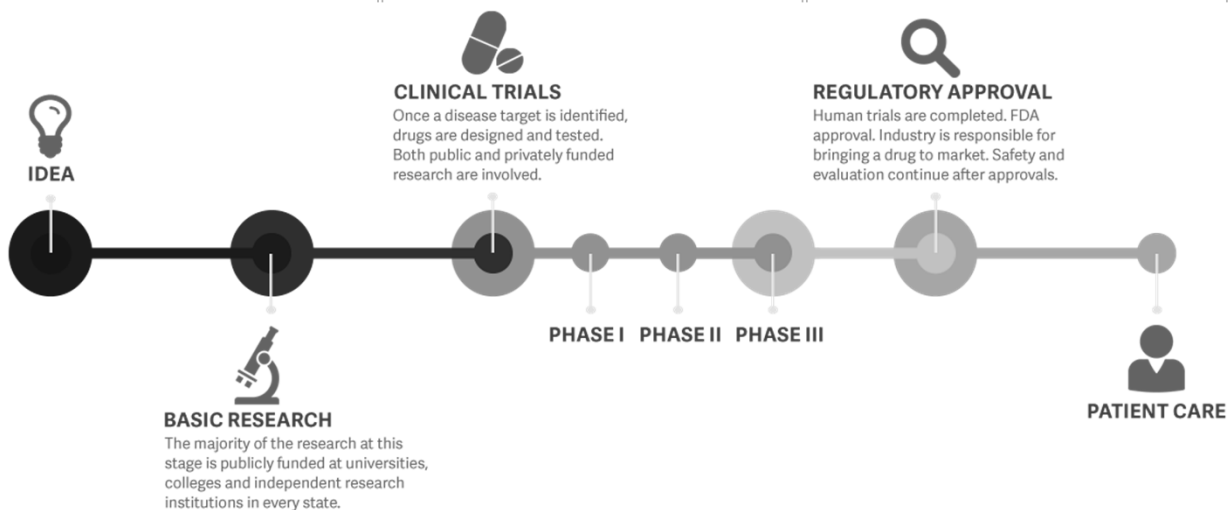
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Biomedical Innovation Development Lifecycle

1. DISCOVERY

2. DEVELOPMENT

3. DELIVERY

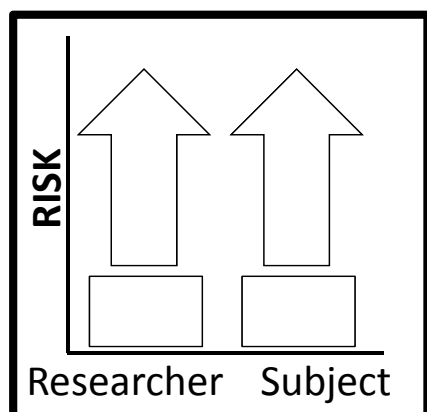


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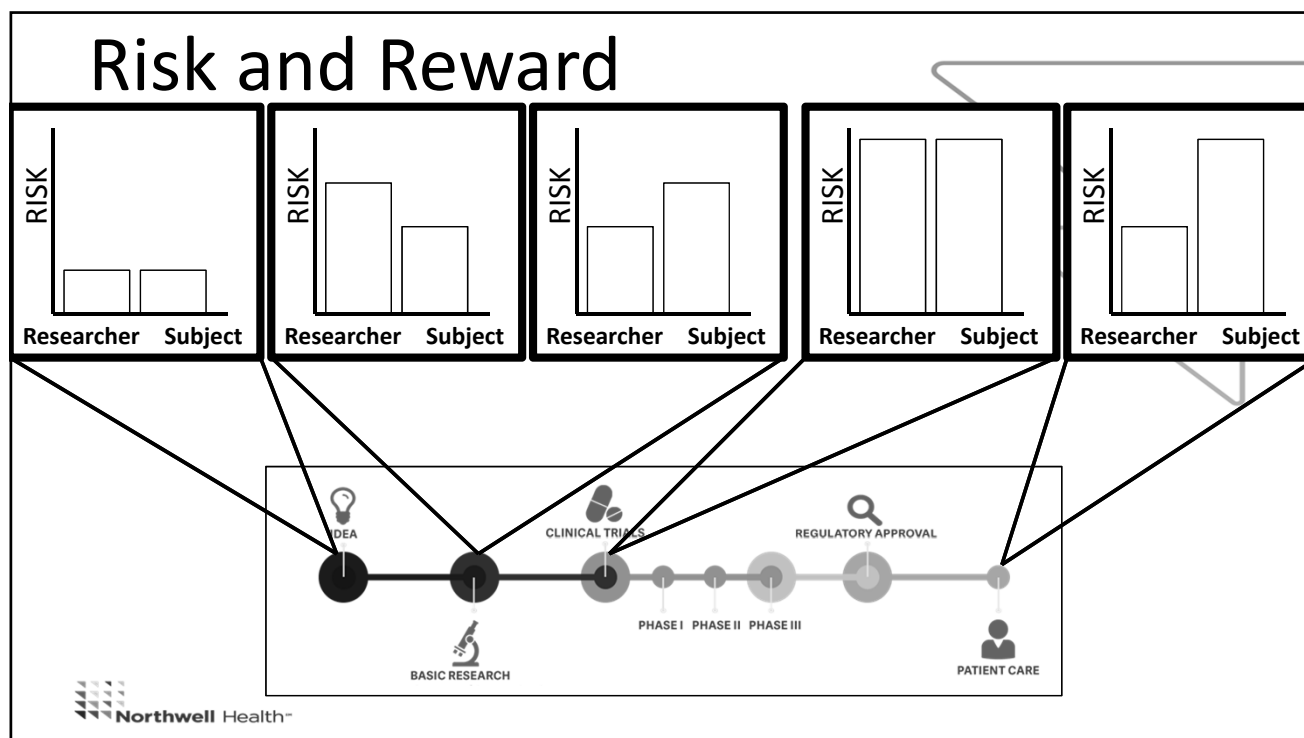
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Risk and Reward

- Risk to both the researcher and subject need to be considered
- Absolute increase v. difference in increase

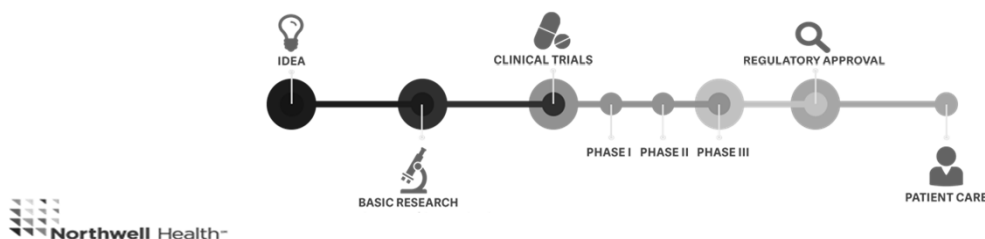


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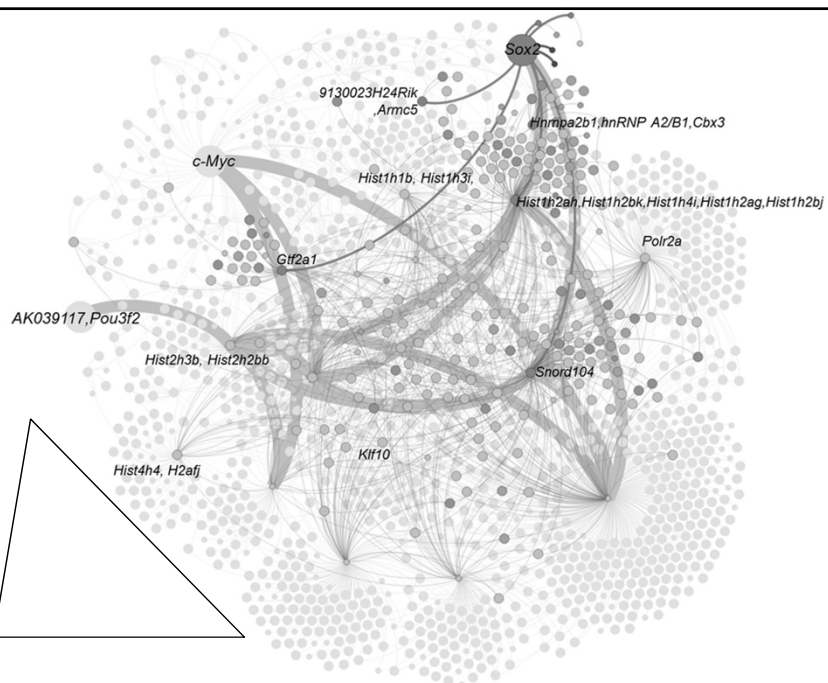


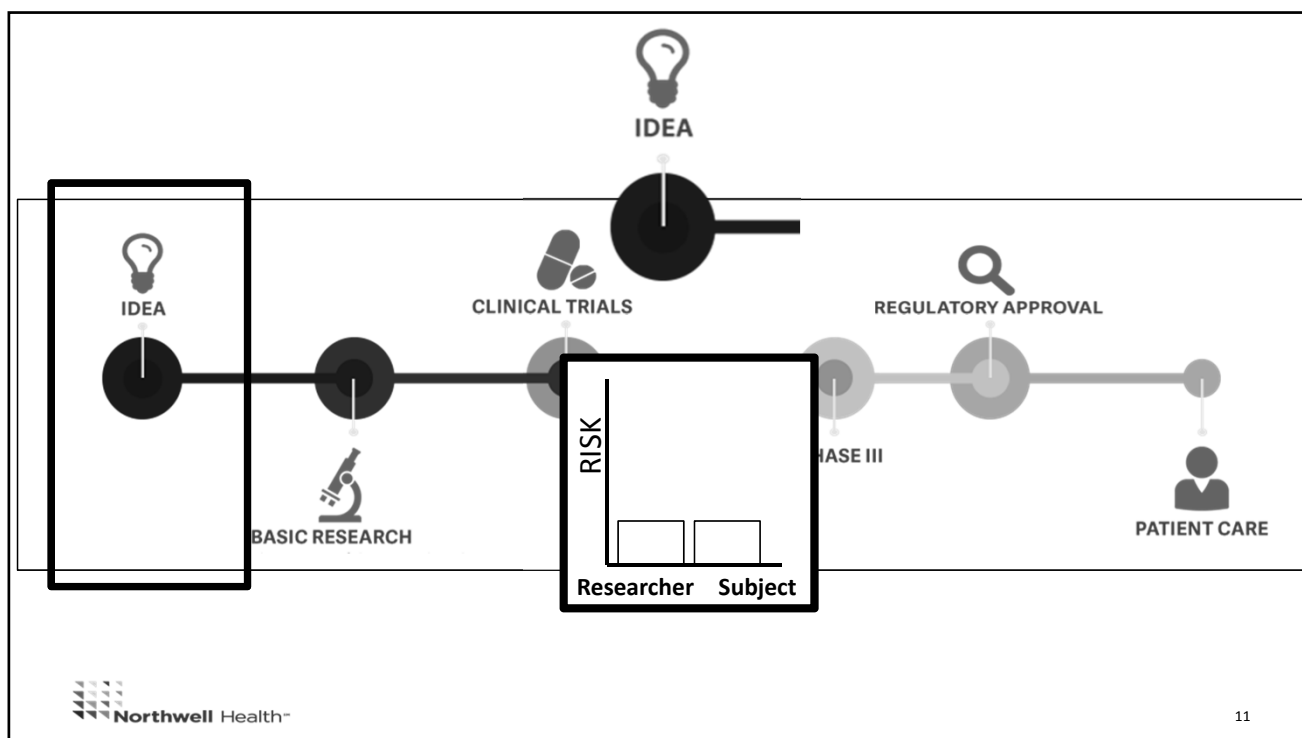
Biomedical Innovation Risk Management

- Risk management requires engagement at all levels of biomedical research
- Establishing standards and maintaining high quality is attractive to outsiders and researchers
- Changing culture is an example of indirect risk management
- Maintaining continued excellence requires ongoing education and outreach



Pre-Clinical Research





Pre-Clinical Research

- What is pre clinical research?
 - Research that does not use human subjects.
 - It can be based on data, biological components, cells, animal, etc.
 - These issues change the risk proposition.
- How does it differ from Clinical Research?
 - Research that requires the use of human subjects.
 - Specifically for safety, efficacy, other experimental questions, etc.
- Who does it ?
 - Academic Institutions, Hospital Systems, Private Institutes, Pharmaceutical Companies, etc.



Risk: Reproducibility

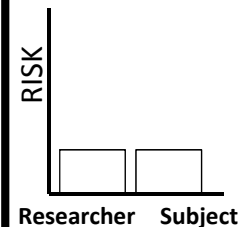
The Office of Research Integrity (ORI) and the NIH have reported problems surrounding data reproducibility.^{1,6}

Reproducibility is a big concern within the biomedical research community. There are a number of factors that lead to this:

- Conceptual weakness and cognitive bias
- Research background and cultural differences
- Internal and external Pressures
- Biological variability
- Experimental design and performance, low quality
- Technical issues
- Presentation



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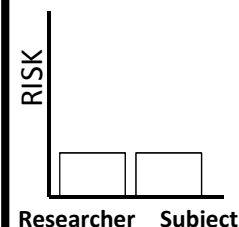
Risk: Reproducibility

Compliance/Risk Management Strategy:

- PI Education; Indirect Strategies
 - GLP-like documentation not always kept
- Ongoing monitoring and intervention of environment (physical and cultural) and equipment
- Give Guidance on methods for PIs to better manage experimental design and data

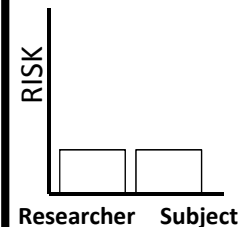


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Case Study #1

In 2011, scientists at Bayer HealthCare in Germany analyzed 67 in-house projects, specifically looking at reproducibility of target discovery (target identification and validation). ²



They focused on main relevant published data, citations, in-house obtained data versus the published data, the impact of the results from the outcome of projects, and models used in experiments and publication.

They found that only ~20-25% of the 67 projects had in-house data completely in line with the subsequent publications.

Their findings support the many examples noted by ORI. Publishing data that cannot be reliable can cause a **ripple effect**.



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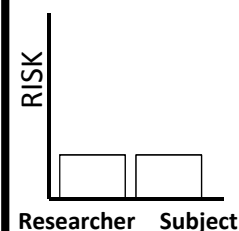
Case Study #1

Problem

- Lack of reproducibility of published drug target data

Ripple Effect

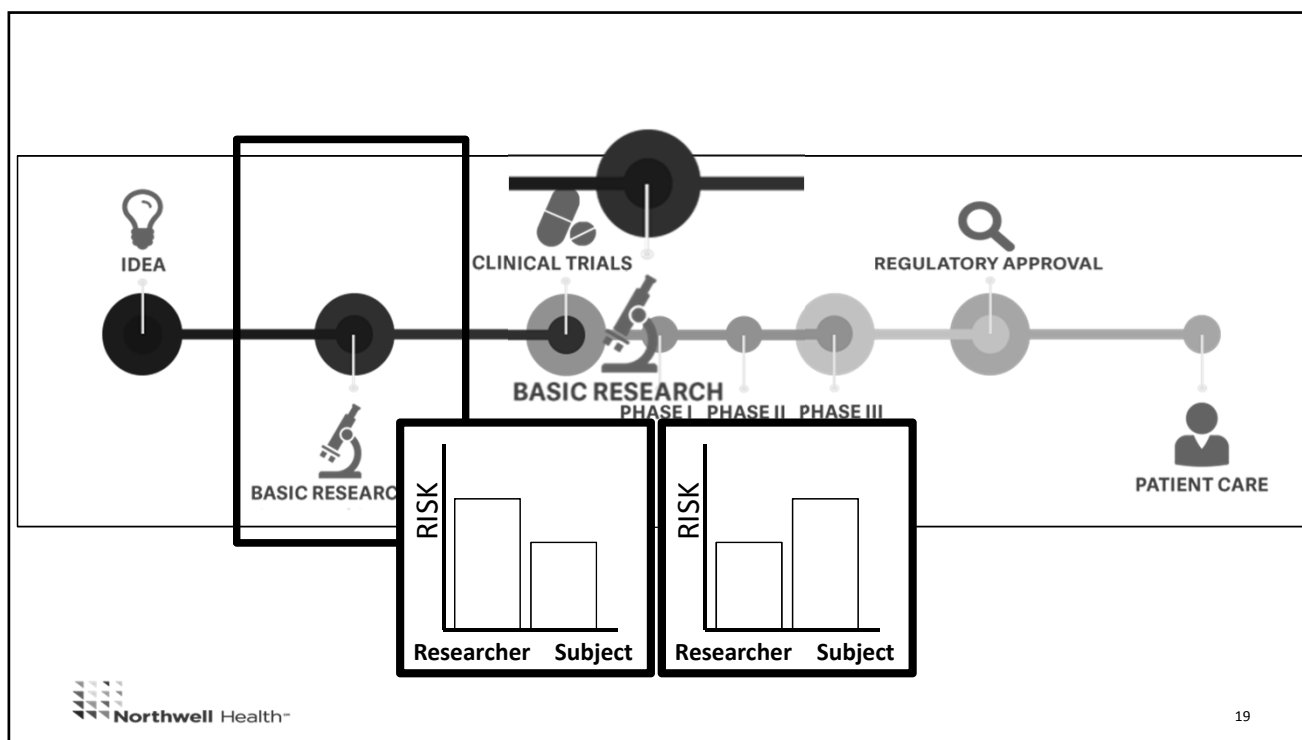
- Cost of drug development skyrockets due to validation needs
- Further support that data being published in journals, including high impact journals, may not be reliable



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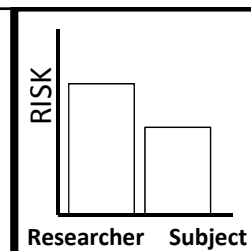
Cells to Animal Models





Cells to Animal Models

- Bridge from the bench to animals
 - Most ideas and concepts are tested in simplified systems
 - Cell Culture, Organoids, Embryonic Tissues, etc.
 - Sooner or later the tested hypothesis becomes too complex for reduced systems
- Moving science forward
 - Animal models contain complex systems and interactions that cannot be modeled
 - Some experiments require complex readouts that include behavior, immune function
 - For example: higher cognitive functioning or complex neural networks

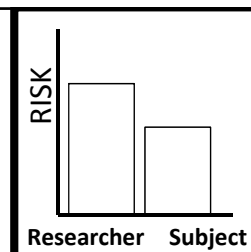


Risk: Research Integrity

- Integrity must be maintained across all phases
 - Preclinical research spans a long timeframe
- One of the first opportunities to shirk evidence
 - Active experimentation is ongoing
 - Evidence might not support hypothesis/theory
- Federal Regulations
 - Pushing for more institutional oversight
 - Better to self monitor than be caught
- **Compliance/Risk Management Strategy:**
 - RCR Training and Ongoing Education
 - Indirect Risk Management



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Case Study #2

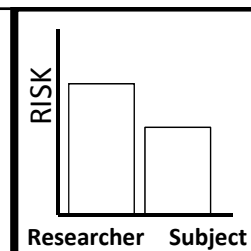
Haruko Obokata of Japan's RIKEN Center for Developmental Biology was found guilty in 2014 of research misconduct.⁹

Nature published two papers authored by Obokata and her team. The papers focused on Stimulus-triggered acquisition of pluripotency (STAP).¹¹⁻¹²

STAP was a novel technique wherein blood cells from neonate mice were subjected to stress, causing them to "reprogram" into pluripotent stem cells that could hypothetically adapt to any environment.



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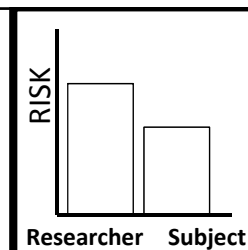
Case Study: #2

Problems

- Misrepresented images comparing mouse embryos
- Doctored an electrophoresis gel image
- Plagiarized and misrepresented methods section

Ripple Effect

- Waste of animal lives by the study team and by others who tried to replicate the data
- Tarnished reputations of those working on the study team unaware of fraud
- Wasted time after RIKEN asked researchers to review all publications (~200,000), utilizing time and resources



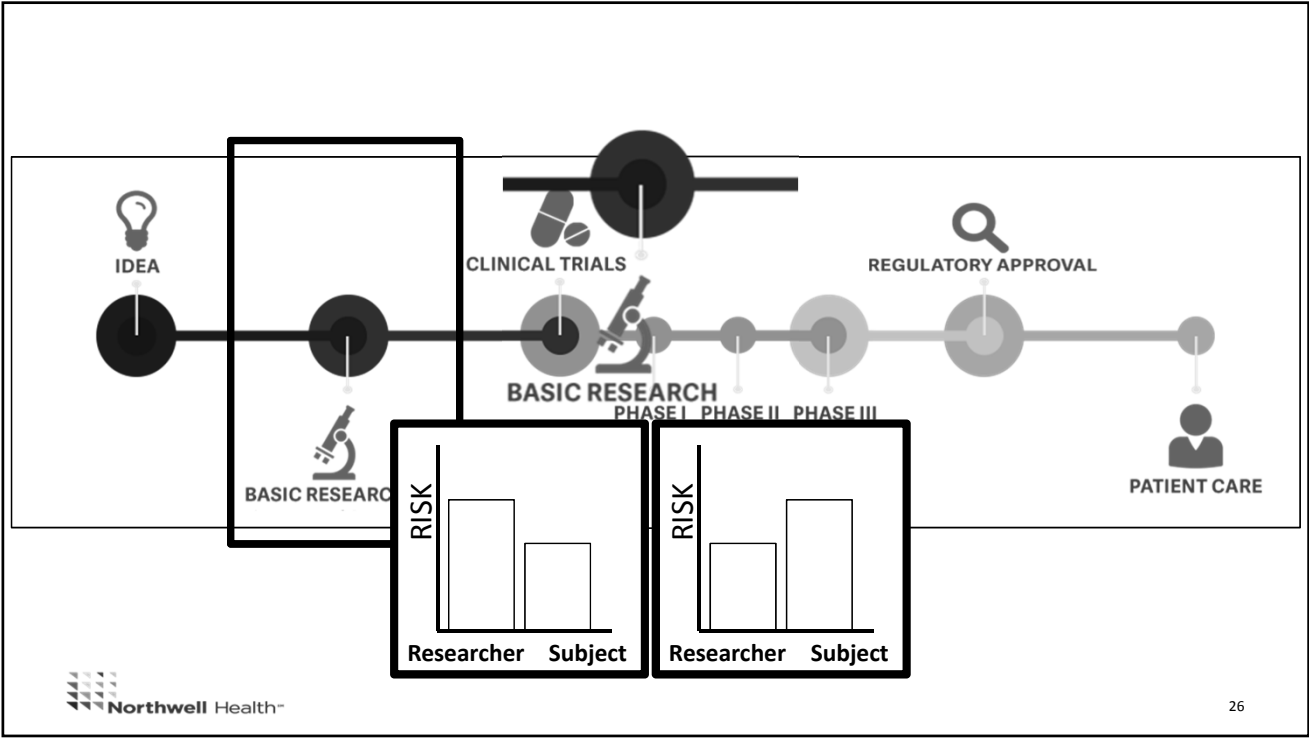
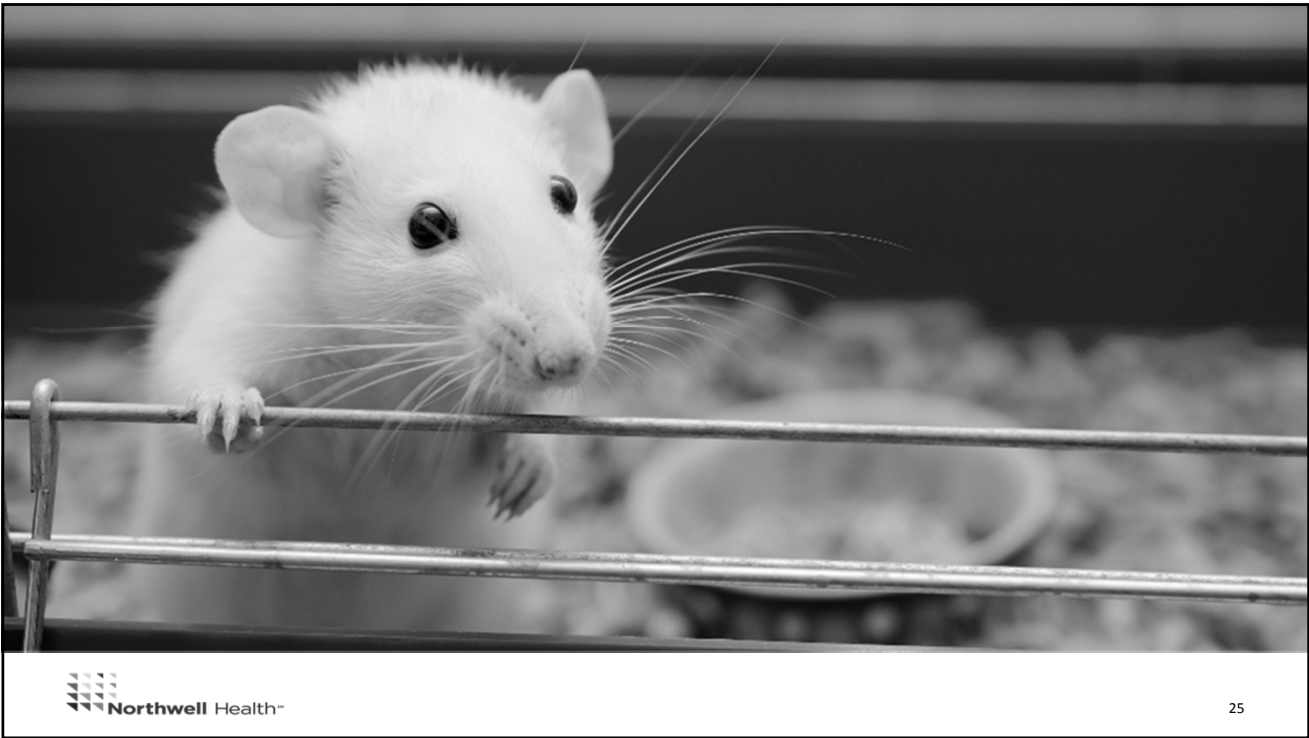
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References: 3-5,9-10

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Animal Welfare

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Animal Welfare

The Animal Welfare Act (AWA)¹⁶, established in 1966, is the Federal law in the United States that protects laboratory animals. Birds, laboratory mice, laboratory rats, farm animals and cold-blooded animals are not covered by the AWA.

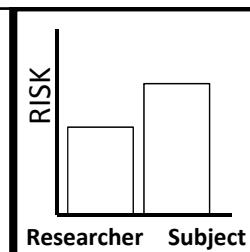
The *Guide for the Care and Use of Laboratory Animals*¹⁷ a.k.a. “The Guide,” produced by The Office of Laboratory Welfare (OLAW), is the gold-standard guidance document that all accredited programs must adhere to.

Over the years, studies have been conducted with the purpose of fine-tuning the balance between animal welfare and good science.

Often overlooked, poor animal care can skew data results.



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Animal Welfare

•Compliance/Risk Management Strategy:

- Close relationship with regulatory committees (IACUC)
 - Consult and give guidance/feedback on the regulatory oversight of the committee
- Close relationship with the operational groups (vivarium/vet services)
 - Consult and give guidance on SOP development and gaps in documentation
- Ongoing Audit Strategy (routine and for cause)
 - Risk Based
- Ongoing Education and Training
 - Extension of audit finding
 - Ethics, Welfare, Techniques



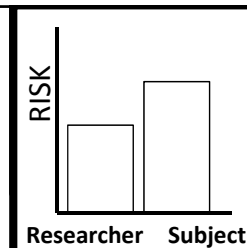
References: 7-8,15

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Risk: Animal Stress and Pain Management

Stress, which can lead to distress, in animals is a very common problem in laboratory animal facilities. Stress comes in many different forms, and the consequences of it range from neutral to catastrophic.



In animal facilities that house large numbers of rodents, management of the conditions within the animal holding rooms as well as the facility at large is critical. Ignoring these conditions can lead to unforeseen consequences.

One source of stress and distress in laboratory models is pain. Scientists who wish to use animal models must take pain management into consideration while developing and performing their studies. Consideration of pain management strategies and reporting is a fundamental concern in laboratory animal care.

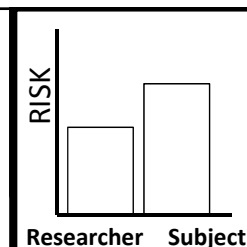
Risk: Animal Stress and Pain Management

For mice, some stressful conditions include:

- Over-handling of mice, including any movement of the cage (changing cages, cleaning cages, monitoring, etc.)
- Excessive noise and/or vibrations (music, construction, etc.)
- Strong odors (pheromones from other cages, perfume on animal husbandry technicians)
- Separating sires from pregnant dams

Resulting in such negative results as:

- Delay of research
- Inability to obtain the amount of specific animals needed for a study
- Loss of financial investment
- Potential waste of animal lives



Case Study #4

Larry Carbone and Jamie Austin of the Laboratory Animal Resource Center at The University of California, San Francisco, published *"Pain and Laboratory Animals: Publication Practices for Better Data Reproducibility and Better Animal Welfare."*

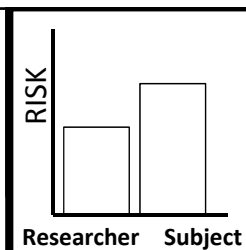
The study addresses a current problem faced by those who perform animal research studies which lead to animal pain.¹⁵

Scientists need to make a choice on pain management in their research animals. Often times, they are faced with a difficult choice which balances animal welfare and experimental data.

- Certain, or any, analgesics or anesthetics may create skewed data
- Withholding analgesics and/or anesthetics may leave the animals in pain, which also may skew data and could become an animal welfare concern
- Scientists are hard-pressed to find accurate, informative data revolving around pain management in published works



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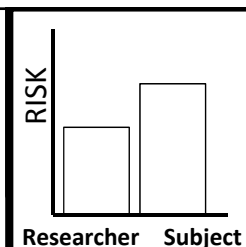
Case Study #4

Problem

- Withholding pain management to avoid data artifacts
- Providing analgesics to the animals in a study without a methodical basis
- Publishing studies with minimal or no information describing why certain pain management was or was not used

Ripple Effect

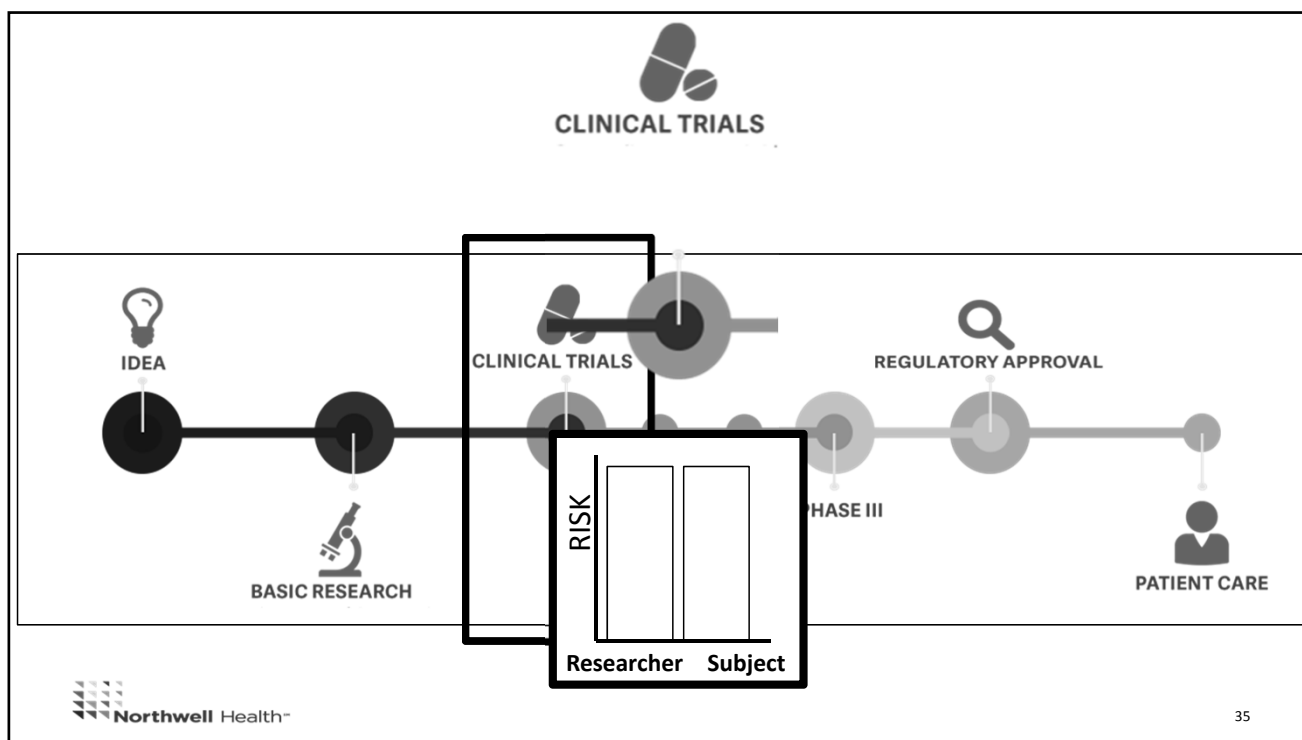
- Potential animal welfare concerns and undue pain
- Under dosing or overdosing animals leading to skewed data
- Continuing the cycle of scientists not being able to make a confident decision in their choice of pain management for a particular study



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Animal Models to Clinical Research



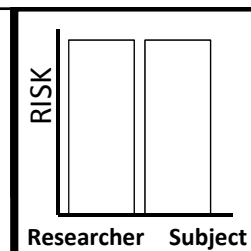


Animal Models to Clinical Research

When making the transition from animal research to clinical research, there are a number of factors that should be thoroughly completed and vetted:

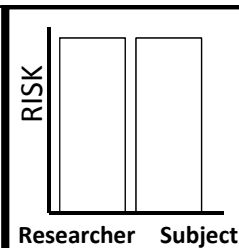
- Repetition of experiments and confirmation of data reproducibility
- Representing pre-clinical data and methods
- Solid experimental design and statistics
- Demonstration of quality citations
- Acknowledging and addressing biological variability

Unfortunately, there have been studies that did not demonstrate strong pre-clinical research methods but were able to move forward to Phase I clinical trials.



Risk: Reliable Data and Human Subject Safety

- Human Subject Rights, Safety and Welfare
 - Focused on Safety at this point
 - Subject safety/welfare hinges on the applicability, reliability, and quality data
 - Potential clinical bias from researchers, new to the lifecycle
 - Concerns for subject rights, safety, welfare drive increased risk to researcher through increased risk to the subject
- Rational research design
 - Bridge to Clinical use
- **Compliance/Risk Management Strategy:**
 - Pre-Clinical to Clinical is the confluence of all previous (data, integrity, quality animal work)
 - Combination of pre and clinical compliance, and regulatory oversight (IRB)
 - Regulatory Affairs (FDA, etc.)



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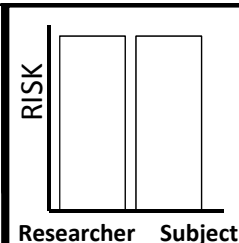
Case Study #5

In 2006, a phase I trial testing a novel CD28 superagonist antibody, TGN1412 began in London. Eight healthy male subjects were placed in a double-blind, randomized, placebo controlled phase I trial.

Within 12 hours of infusion, one subject experienced multi-organ failure. Between 18-21 hours post-infusion, five additional subjects also experienced multi-organ failure. The two subjects who were unharmed received placebo.

Reliance on Non Human Primate (NHP) data.

The cause of the adverse reactions was hypercytokinemia (cytokine storm), which is an uncontrollable immune response.



References: 13-14

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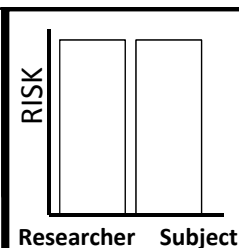
Case Study #5

Problems

- Insufficient *in-vitro* tests on human material
- Relying solely on NHP data for human dose calculations
- Ignoring subtle changes in cytokine levels in NHP subjects
- All human subjects received their infusions at the same time

Ripple Effect

- Improper dose calculations for human subjects
- Failure to anticipate and prepare for adverse events in humans
- Loss of human subjects' protection
- Waste of animal lives



References: 13-14

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Conclusions

1. Drug and device development is a lengthy process, and each step has unique considerations.
2. Good science is key:
 - Consider the risk and mitigation strategies for data, cells, animal models and human subjects
3. Ensure a good compliance and risk management program is in place and constantly adjusted.
 - Reviews, Education, and Policy making

References

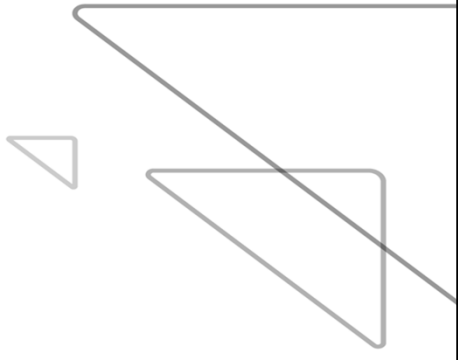
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Q&A

Q&A





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