

# Research Ethics Cases

Leslie I. Katzel, MD, PhD

Director, Baltimore VAMC GRECC

Associate Professor of Medicine, UMSOM, UM-OAIC

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With assistance of slides from Alan K. Jacobson, MD,  
Brenda Cuccherini, Ph.D, MPH

# Talk outline

- Presenting a number of cases and scenarios involving breaches in research and professional ethics, research misconduct, and research ethical issues

# Case #1: Disgraced med school dean fired over sordid allegations (NYT July 21, 2017)



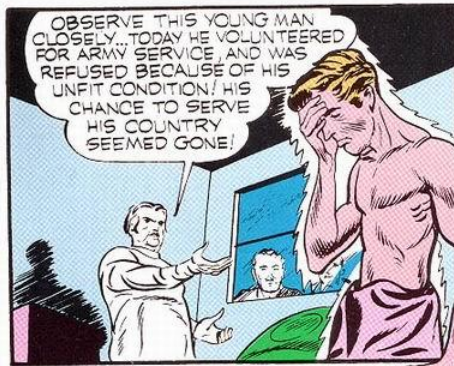
- Puliafito, 66, resigned from his \$1.1 million-a-year job at the University of Southern California's Keck School of Medicine in March 2016 — three weeks after a 21 year old prostitute overdosed in his hotel room
- Puliafito helped bring in \$1 billion in donations, raised the school's prestige and profile, and oversaw hundreds of staff members and students.
- Meanwhile, at night, he was bringing hookers and addicts into his office at USC to party: Photos show the drugged-up doc's party posse smoking heroin in Keck School lab coats and USC merchandise, the Times reports
- After the incident he went to work for New York pharma firm Ophthotech — which laid him off in December when its drugs failed clinical trials.
- Puliafito then went back representing USC at public events — and seeing patients at the university's eye clinics
- Finally fired in July after Puliafito was seen on video apparently smoking methamphetamine and consorting with addicts and criminals.

# Case #2: Military experiment

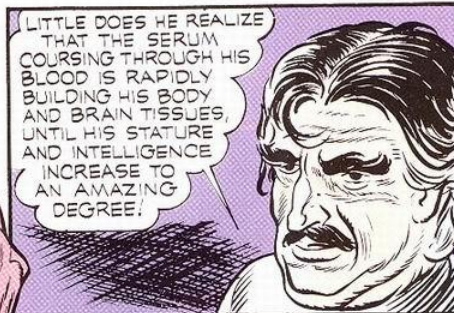
- Just prior to WW II the US military was interested in developing a serum that could create enhanced humans who would be super soldiers. A sickly man (SR) who was “4F” and could not serve in the military apparently volunteered for this phase I first in human experiment. It is not documented as to whether he signed written informed consent or whether there were prior animal studies that supported the research.

Artist interpretation of the experiment (Simon and Kirby Captain America #1)





OBSERVE THIS YOUNG MAN CLOSELY... TODAY HE VOLUNTEERED FOR ARMY SERVICE, AND WAS REFUSED BECAUSE OF HIS UNFIT CONDITION! HIS CHANCE TO SERVE HIS COUNTRY SEEMED GONE!



LITTLE DOES HE REALIZE THAT THE SERUM COURSING THROUGH HIS BLOOD IS RAPIDLY BUILDING HIS BODY AND BRAIN TISSUES, UNTIL HIS STATURE AND INTELLIGENCE INCREASE TO AN AMAZING DEGREE!



THE PEOPLE IN THE OBSERVATION ROOM GAPE IN WONDER AT THE SCENE BEFORE THEM!

WH-WHY, LOOK...

HE... HE'S CHANGING!

IT... WORKS...  
...IT... WORKS!



IT IS WORKING! THERE'S POWER SURGING THROUGH THOSE GROWING MUSCLES... MILLIONS OF CELLS FORMING AT INCREDIBLE SPEED!



(BEHOLD!) THE CROWNING ACHIEVEMENT OF ALL MY YEARS OF HARD WORK! THE FIRST OF A CORPS OF SUPER-AGENTS WHOSE MENTAL AND PHYSICAL ABILITY WILL MAKE THEM A TERROR TO SPIES AND SABOTEURS!



WE SHALL CALL YOU CAPTAIN AMERICA, SON! BECAUSE, LIKE YOU-- AMERICA SHALL GAIN THE STRENGTH AND THE WILL TO SAFEGUARD OUR SHORES!



but THE HAND OF DEMOCRACY'S ENEMY REACHES DEEP INTO THE RANKS OF AMERICA'S HIGH OFFICIALS... ONE OF THE ARMY MEN WITNESSING THE DEMONSTRATION IS IN THE PAY OF HITLER'S GESTAPO!

I'M AFRAID THIS IS ONE EXPERIMENT THAT MUST NEVER REACH ITS FINAL TEST!



# Ethical /regulatory issues

- Would any IRB approve this study?
- Was he part of a vulnerable population (soldier)?
- Experiment conducted prior to Declaration of Helsinki and Nuremberg Code
- Subject apparently gave verbal consent
- Ethical to attempt to create enhanced humans?

# Case #3: Medical device

- A civilian contractor (AS) is mortally injured in a battlefield injury in the far east. There are no established effective medical treatment. The civilian works with another scientist to develop a new artificial circulatory assist device that would keep him alive. The greater than minimal risk experimental device was used to keep the civilian alive.



Artist interpretation (Leiber and Kirby Tales of Suspense 39)

# Ethical /regulatory issues

- Humanitarian use device? (FDA invasive medical device) not intended for marketing
- Research?
- Private not federally funded performed overseas-not clear if any US regulatory oversight would apply
- Numerous other historical examples where investigators served as study subjects

## Case #3: Alexander Neumeister, MD, Receives Outstanding Scientific Achievement Award from the International Society for Traumatic Stress Studies

- “ NYU Langone Medical Center is pleased to announce that Alexander Neumeister, MD, professor of psychiatry and radiology, was honored with the Robert S. Laufer, PhD, Memorial Award for Outstanding Scientific Achievement by the International Society for Traumatic Stress Studies (ISTSS) Awards Committee, bestowed annually upon an individual or group who has made an outstanding contribution to research in the field of traumatic stress. Dr. Neumeister will receive this award at the ISTSS 28th Annual Meeting, November 1-3, 2012, in Los Angeles, CA.
- “Our outstanding faculty have a long-standing legacy of innovation, and we are thrilled that the important research Dr. Neumeister is doing on PTSD has been recognized by the ISTSS,” said Dafna Bar-Sagi, PhD, senior vice president and vice dean for Science and chief scientific officer at NYU School of Medicine”

# Alexander Neumeister, MD



# NYU closes PTSD studies after complaints from drug regulator (BMJ 2016;354:i3891)

- Eight studies into an experimental drug to treat post traumatic stress disorder (PTSD) have been halted by NYU and the PI has resigned after a letter from the FDA warned that lapses in the conduct of the research jeopardized “subject safety and welfare, and raised concerns about the validity and integrity of the data collected at [the] site.”
- The studies, sponsored by Pfizer, were trials of a fatty acid amide hydrolase (FAAH) inhibitor, a drug with effects on cannabinoid receptors, as a potential treatment for distress in patients with traumatic memories.
- The FDA warning came in a letter to the studies’ PI Alexander Neumeister
- Neumeister was suspended after an investigation by the university’s school of medicine and resigned soon after, though he continues to disagree with the university about the gravity of the alleged violation.
- NYU suspended Neumeister after learning of the FDA’s conclusions—which included allegations that the researcher failed to follow up in a timely fashion with patients who had received the drug, and that he had forged a colleague’s name on study reports.

# Case #4: AIDS researcher sentenced to jail for fraud



- “DONG-PYOU HAN needed impressive lab results to help his team at Iowa State University move forward with its work on an AIDS vaccine — and to continue receiving millions of dollars in federal grants. So Dr. Han did what many scientists are probably tempted to do, but don’t: He faked the tests, spiking rabbit blood with human proteins to make it appear that the animals were responding to the vaccine to fight H.I.V.” (NYT 7/10/2014)

- The falsification made it appear that rabbits immunized with the gp41-54 moiety of the HIV gp41 glycoprotein induced antibodies capable of neutralizing a broad range of HIV-1 strains, when the original sera were weakly or non-reactive in neutralization assays. Falsified neutralization assay results were widely reported in laboratory meetings, seven (7) national and international symposia between 2010 and 2012, and in grant applications and progress reports P01 AI074286-03, -04, -05, and -06; R33 AI076083-04; U19 AI091031-01 and -03; and R01 AI090921-01.

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-037.html>

- As a result of this apparent positive result, Han and his team received approximately \$19 million in grant money from NIH
- James Bradac, who oversees AIDS grants for the National Institutes of Health, called it "the worst case of research fraud he'd seen in his more than two decades at the agency
- In June 2014, as a result of his receiving grant money due to falsified results, Han was indicted on four, federal felony counts of making false statements
- Han pleaded guilty in federal court in February 2015
- On 1 July 2015 Han was sentenced to 57 months imprisonment for fabricating and falsifying data in HIV vaccine trials. He was also fined US\$7.2 million and will be subject to three years of supervised release after he leaves prison.

# Case #5

- In 1997, DN, a graduate student at University of Vermont was hired part time to analyze data and coauthor papers by renown obesity researcher Dr. Eric Pohelman at the University of Vermont
- In Oct 2000, DN was asked to analyze preliminary results from the Vermont Longitudinal Study of Aging that examined the effect of menopause on risk factors for heart disease

# Eric Poehlman, PhD



- Poehlman had hypothesized that women's health would broadly decline after menopause
- DN preliminary analysis showed that some women actually improved their health and cardiac risk factors
- Dr. Poehlman, took the computer disk home for the weekend, reanalyzed the data and got substantially different results that confirm his hypothesis

- Initially DN assumed it was his mistake, but when he examined the revised analyses performed by Poehlman, he recognized that Poehlman had reversed some of the post data with the pre data when the post data was better than the pre to bolster his findings
- What would you have done if you were DN?
- Extensive investigation was ultimately initiated into possible scientific misconduct
- <http://www.ori.dhhs.gov/content/case-summary-poehlman-eric-t>

- From 1992 to 2000, Poehlman received \$2.9 million in federal research funding based on fabricated research data intended to make his work sound more promising. During the period, he filed 17 fraudulent grant proposals to study the impact of menopause on women's health, the benefits of hormone replacement therapy, and other topics.

- Poehlman fabricated test results for all but three of the 35 women in his long-term study of the health effects of menopause, an influential paper indicating that women rapidly lose muscle mass, and gain fat after menopause. The Annals of Internal Medicine retracted Poehlman's findings in 2003 after the University of Vermont found evidence of fraud.
- 10 papers were ultimately withdrawn, including several published when he was at UMSOM

- During the University of Vermont investigation of Poehlman's research fraud in 2000-2001, the US attorney in Burlington found that he "destroyed electronic evidence . . . presented false testimony, presented false documents, and influenced other witnesses to provide false documents."

	Reversed value(s)			
	Falsified value			
	Fabricated value			
	BodyComp&EE		Revised TEE's	
First	TEE-1	TEE-2	TEE1	TEE2
jean		2043.00	2399	2043
ray			3069	2923
beth			3728	3404
seth	2460.00	1838.00	2460	1838
alice		2750.00	2950	2750
thomas	2540.00	2945.00	2945	2540
david			3392	3312
harry		3423.00	3423	2655
frances		1854.00	2377	1854
john		2147.00	3244	2147
anita			2680	2399
carol			2136	2130
anthony	2919.00	3264.00	3264	2919
ron		2950.00	3593	2950
patrick		3221.00	3453	3221
walter			4445	3873
tom		2545.00	3001	2545
john		2723.00	3541	2723
ann		2351.00	2201	2351
mary	2638.00	2227.00	2638	2227
derroll		4056.00	4314	4056
jean		3350.00	3473	3350
lloyd			3593	3410
david		3760.00	3991	3760
berenice		2611.00	2898	2611
david			3837	3471
hild	2328.00	2518.00	2518	2328
elliott		2822.00	3739	2822
ann	2045.00	2359.00	2359	2045
	4722.00		4722	4655

Dr. Poehlman's changes to total energy expenditure values included many fabrications (blue) and reversals of visit one and visit two values (red). The net effects were to greatly inflate the number of subjects and to reverse the apparent effect of aging.

	BodyComp&EE		Revised TEE's	
	TEE-1	TEE-2	TEE1	TEE2
Count	55.00	109.00	135	135
Mean	2391.09	2658.07	2925.97037	2624.57037
Std. Dev.	618.53	640.12	645.699389	613.445074

- Poehlman's admission of guilt came after more than 5 years of investigation, during which time he denied the charges against him
- He pled guilty in an attempt to avoid being the first researcher to be sent to prison for scientific misconduct

# Poehlman

- Barred for life from receiving federal funding
- Pay back \$180,000
- Pled guilty to criminal charges of fraud
- Retracted 10 articles
- Faced up to 5 years of jail time
- Sentenced to a year and a day for making a false statement on his grant application

# The Spectrum of Research Impropriety

Administrivia

Fatal / Criminal



administrivia - the tiresome but essential details that must be taken care of and tasks that must be performed in running an organization; "he sets policy and leaves all the administrivia to his assistant" TheFreeDictionary



# Research Impropriety: What is it?

## Multitude of Terms

- Research or Scientific
  - Impropriety
  - Misconduct
  - Misbehavior
  - Noncompliance
  - Fraud
- Sloppy science / research
- Junk science / research
- “Egregious abrogation of investigator responsibilities”
- “Scientists behaving badly”

# Research Impropriety: Why does it occur?

- Why wouldn't it happen? It happens in all other human activities.
- Pressure to publish.
- Inadequate training. Not taught good practice. Indeed, sometimes taught the opposite.
- Does sloppy behaviour spill over to fraud?
- You can get away with it. The system works on trust.

Dr. Richard Smith  
Former Editor, British Medical Journal

# % of scientists who say that they engaged in the behavior listed within the past three years (Survey of ~1800 NIH funded scientists)

1.	<b>Falsifying or 'cooking' research data</b>	0.3%
2.	<b>Ignoring major aspects of human subject requirements</b>	0.3%
3.	<b>Not properly disclosing involvement in firms whose products are based on one's research</b>	0.3%
4.	<b>Relationships with students, research subjects or clients that may be interpreted as questionable</b>	1.4%
5.	<b>Using another's ideas without permission or due credit</b>	1.4%
6.	<b>Unauthorized use of confidential information in connection with one's own research</b>	1.7%
7.	<b>Failing to present data contradicting one's own previous research</b>	6.0%
8.	<b>Circumventing minor aspects of human subject requirements</b>	7.6%
9.	<b>Overlooking others' flawed data or questionable interpretation of data</b>	12.5%
10.	<b>Changing the design, methodology or results of a study in response to pressure from a funding source</b>	15.5%

# Survey of 187 UK-based academics engaged in research in the biological sciences

Respondents' ranking of unethical behaviours, 1 being the most serious and 5 being the least serious.

Behaviour	Average ranking	Agreement with ranking (%)
Fabricating data	1.6	76.3
Plagiarism	2.5	53.8
Taking someone else's idea	3.1	43.7
Over-selling of results	3.6	38.3
Inappropriate co-authorship	4.3	62.9

Roberts and St. John (2014), Estimating the prevalence of researcher misconduct: a study of UK academics within biological sciences. PeerJ 2:e562; DOI 10.7717/peerj.562

# Research Misconduct

- In a meta-analysis of scientific misconduct, Fanelli (2009) found that estimates of fabrication and falsification ranged from 0.3 to 4.9% with a weighted mean of 1.97%
- the estimated prevalence of plagiarism may be 4%.
- Inappropriate co-authorship in one study that was ranked the least serious issue was the most prevalent (68.7%) UCT) (Roberts Peer J 2014),

# The Cost of Research Impropriety I

- Research Integrity Cost
    - Scientific Record
    - Public Confidence
- “Impropriety of any type in the conduct of research is abhorrent to the inherent purpose of all scientific inquiry: the discovery and dissemination of truth.”

# The Cost of Research Impropriety (2)

- Direct Investigative and Management Cost
- Cost to research subjects and patients
- Distraction Cost
  - What isn't getting done while resources are utilized to investigate and manage the impropriety and its fallout.

# Research Impropriety

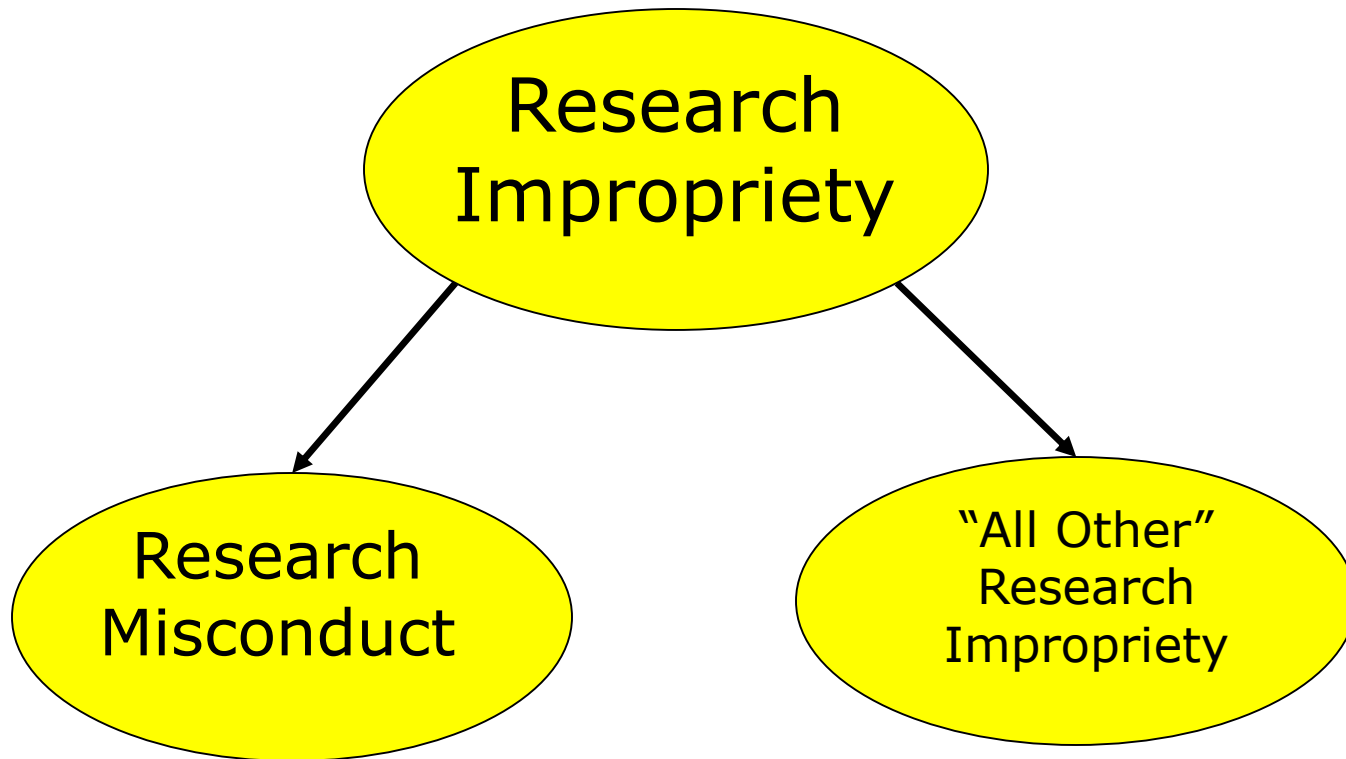
So, What IS it?

# Definition of Research Impropriety Under VHA Handbook 1058.2

“Research impropriety is any ethical lapse or other impropriety involving or occurring in connection with research other than research misconduct...” as defined in the Federal Policy on Research Misconduct

VHA Handbook 1058.2 “Research Misconduct”

# Types of Research Impropriety



# Research Misconduct: VHA Policy Conforms to Federal Policy

- Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
- Research misconduct does not include honest error or differences of opinion.

Federal Register Notice Vol. 65, No. 235, Dec. 6, 2000

# Research Misconduct: Definitions

- **Fabrication (1058.2 - 5c)**
  - Making up data or results and recording or reporting them
- **Falsification (1058.2 - 5d)**
  - Manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record
- **Plagiarism (1058.2 - 5i)**
  - Appropriation of another person's ideas, processes, results, or words without giving appropriate credit

# Research Misconduct: Definitions II

- Federal and VHA definitions are extremely precise
- Research Misconduct is specifically restricted to FFP
- Non-federal institutions, i.e. affiliated universities, may have variable policy definitions, even though they are required to follow federal policy on federally funded projects

# Research Misconduct: How Should Allegations be Handled?

- VA Handbook 1058.2 identifies individuals responsible for investigating allegations of misconduct and provides guidance for procedures and roles.
- Responsible authorities must determine whether the conduct was deliberate, or honest error.
- Investigations must be conducted confidentially and with discretion to protect both informant and accused parties.

# Research Misconduct: Management

- Defined Phases
  - Allegation
  - Inquiry
  - Investigation
  - Adjudication
  - Departmental Review
  - Appeals

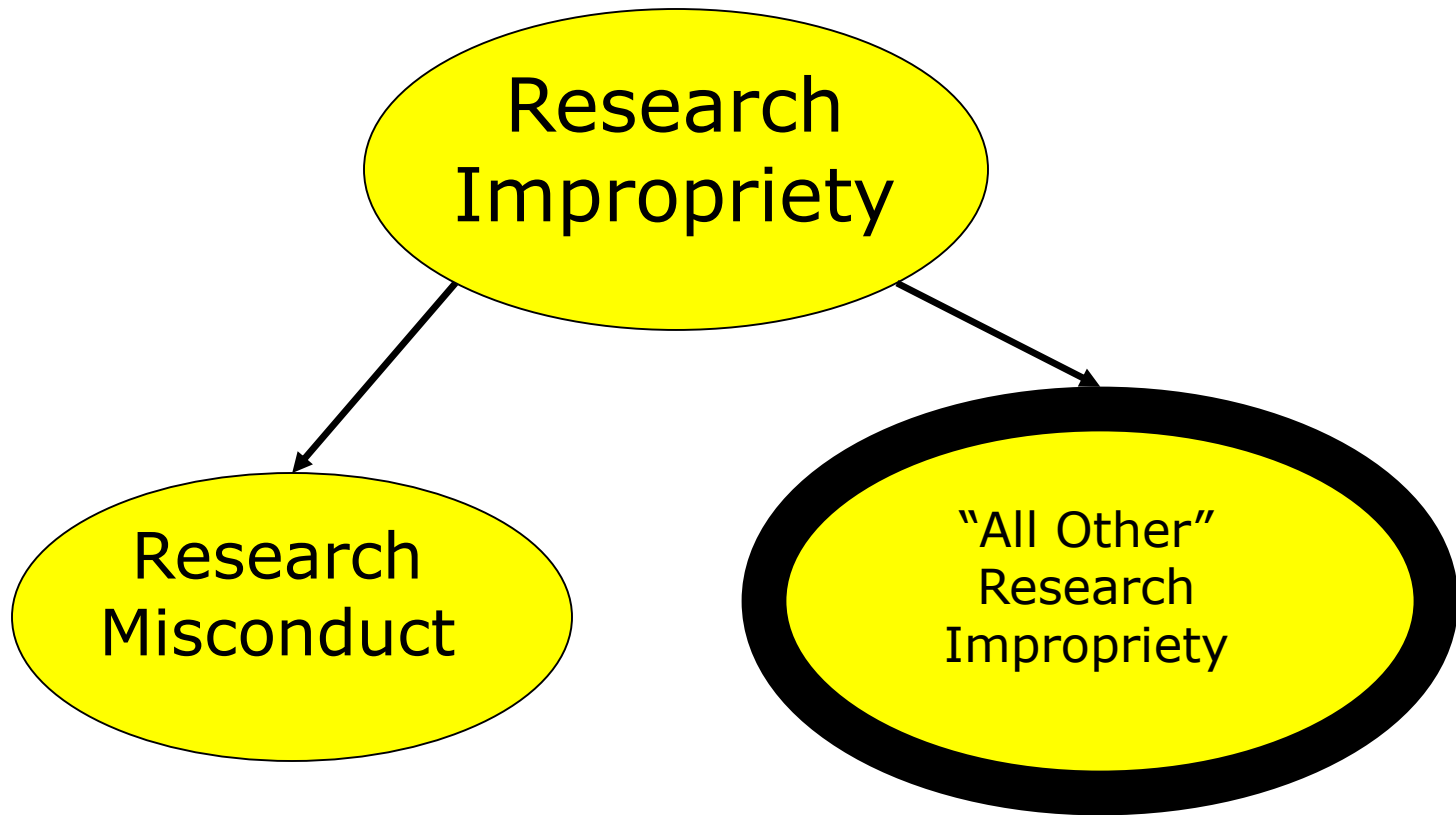
# Research Misconduct: Corrective Actions - Considerations

- The extent of the misconduct (amount, duration, scope)
- Degree to which the misconduct was knowing, intentional or reckless
- Presence or absence of a pattern of misconduct
- The consequences or possible consequences of the misconduct
- The respondent's position and responsibility for the project
- Cooperation of the respondent during Inquiry and Investigation
- Likelihood of rehabilitation
- Presence of similar cases - commensurate action
- Any other extenuating or aggravating circumstances

# Research Misconduct: Examples of Corrective Actions

- Government-wide debarment (in development)
- Removal from a particular project, suspend/terminate award
- Restitution of funds or civil penalties
- Prohibition from receiving VA research funds for a period
- Correction or retraction of published article
- Monitoring or supervision of future work
- Required certification of data
- Required certification of sources (references and contributors)
- Remedial education or mentoring

# Types of Research Impropriety



# “All Other” Research Impropriety: Definitions / Examples

“Examples of research impropriety include, but are not limited to, conflicts of interest, misallocation of funds, sexual harassment, discrimination, and breaches of human subjects protections and animal welfare requirements.”

VHA Handbook 1058.2 “Research Misconduct”

# “All Other” Research Impropriety: Examples

- Failing to retain significant research data for a reasonable period;
- Maintaining inadequate research records, especially for results that are published or are relied on by others;
- Conferring or requesting authorship on the basis of a specialized service or contribution that is not significantly related to the research reported in the paper;
- Refusing to give peers reasonable access to unique research materials or data that support published papers;

# “All Other” Research Impropriety: Examples

- Engaging in inappropriate authorship practices on a publication and failing to acknowledge that data used in a grant application were developed by another scientist
- Inappropriate data analysis and use of faulty statistical methodology
- Failure to document and incorporate subject’s feedback in findings
- Misuse or misallocation of funds for unauthorized purposes
- Financial conflict of interest of self or close relatives (e.g., spouse)
- Time and effort reporting errors or omissions or over-commitment
- Inappropriate staff assignments
- Neglect of research-related administrative tasks

# “All Other” Research Impropriety: Compromise of Research Subject Protections

- Inadequate adverse event reporting
- Privacy violations
- Breach of patient confidentiality
- Failure to ensure that subjects understand informed consent
- Failure to conduct adequate literature review prior to starting clinical trials

- Failure to inform subjects of new information
- Failure to warn subjects of possible side effects

# Research Impropriety: Can it be Prevented?

- Educate - Training
  - GCP, HRP, HIPAA, Privacy
- Verify - Monitoring and Audits
  - Routine
  - For-cause
- Provide a compliant environment
  - Accreditation
  - Exemplary Leadership
  - Culture of Responsible Research
  - Culture of Compliance

# Finding the Balance

- Effective assurance of “responsible conduct of research”
- Suffocating oversight and bureaucracy

# Case #6

- An investigator is performing a small randomized control trial examining the impact of 2 different nutritional supplements versus usual care on weight and 6 month mortality in older nursing home patients.
- Many of the subjects have dementia and are unable to provide their own consent, therefore consent is obtained from their legally authorized representative (LAR), as well as assent from the subject

- As part of a routine audit by the IRB, it is noted that in 35 of 107 individuals enrolled, the PI has not provided any documentation in the chart as to the relationship of the LAR to the subject (required by the IRB), and for 22 subjects, the individual signing as LAR had been misidentified, i.e. friend of the person signing in place of the daughter, etc.

- The audit findings are reviewed by the convened IRB
- What determinations will they make?
- What is the corrective action plan?
- Can the PI use the data?

# IRB determinations

- Non-compliance
- Serious non-compliance
- Continuing non-compliance
  
- All of these determinations will result in the investigator developing and implementing a corrective action plan
- Other remedial and regulatory actions may be taken

- Example of serious non-compliance
- Use of data?

# Case #7

- A research subject is enrolled in a phase 3 RCT that involves getting a monthly infusion in the outpatient setting of the experimental agent
- The study nurse administers the drug over 10 minutes instead of our an hour as written the protocol and the patient becomes hypotensive and requires fluid resuscitation and admission to the ICU

- The PI reports the incident to the IRB
- What determinations does the IRB make?

- Failure to follow the protocol as written
- Unanticipated problem involving risk to subject or others
- Queries the PI on the corrective action plan

# Research misconduct-peer review

## **Major publisher retracts >250 scientific papers amid wider fake peer-review scandal**

- Biomed Central a major publisher of scholarly medical and science articles has retracted >250 papers because of “fabricated” peer reviews amid signs of a broader fake peer review racket affecting many more publications (<http://retractionwatch.com/2015/08/19/17-retractions-from-sage-journals-bring-total-fake-peer-review-count-to-250>)

# Scholarly journal retracts 60 articles, smashes ‘peer review ring’

- In 2013, the editor of Journal of Vibration and Control (JVC), Ali H. Nayfeh, became aware of people using “fabricated identities” to manipulate an online system called SAGE Track by which scholars review the work of other scholars prior to publication
- JVC determined the ring involved “aliases” and fake e-mail addresses of reviewers — up to 130 of them — in an apparently successful effort to get friendly reviews of submissions and as many articles published as possible by Chen and his friends. “On at least one occasion, the author Peter Chen reviewed his own paper under one of the aliases he created,” according to the SAGE announcement

# Conclusions

- Well-designed human subject research yields powerful, generalizable knowledge helpful to future patients
- There is a lengthy history of abuses, leading to safeguards codified in the Nuremburg Code and Declaration of Helsinki, as well as Code of Federal Regulations
- Everyone involved in research is responsible for upholding these ethical principles (local accountability)