Research ethics and research integrity

LIZA DAWSON, PHD MA

JULY 24, 2018

MAHIDOL UNIVERSITY, BANGKOK

Disclaimer

The opinions presented are those of the speaker and not official views of the US National Institutes of Health or other US government agencies

Introduction:
What happens when things go wrong

Werner Bezwoda: South African researcher studying breast cancer treatments for patients with high risk breast cancer

In 1999, Bezwoda reported his study bone marrow transplantation plus high dose chemotherapy versus standard care in a trial of approximately South African 150 patients

Bezwoda reported that the experimental treatment was highly effective in reducing disease progression and mortality

Results reported by Bezwoda

Bezwoda's report at ASCO, May, 1999

	High dose	Standard	p
Relapsed	19/75	52/79	<0·001
Died	8/75	28/79	<0·01
Relapse-free survival	400+ weeks	190 weeks	<0·05
Overall survival	400+ weeks	320 weeks	<0·05

Modified from *Proc ASCO* 1999; **18:** A4.

Results of an audit

Bezwoda had not properly documented inclusion criteria, randomization, or treatment assignment

Many patient records were missing; numerous patients did not meet eligibility criteria

There were serious deviations from the protocol; control group patients did not receive the reported treatment

There was no ethics committee review or informed consent

Conclusion of auditing group:

"The multiple publications of this study do not report verifiable data, and nine other publications coauthored by the principal investigator contain at least one major untrue statement."

Impact: early positive trials of bone marrow transplant for breast cancer

- A few small studies of high dose chemotherapy and bone marrow transplant had reported positive findings, in addition to Bezwoda
- Other researchers attempted to conduct properly randomized trials of bone marrow transplantation
- Patients were reluctant to accept randomization due to their belief that the treatment was effective;
- **Eventually after completed trials, bone marrow transplantation was found to be ineffective for this condition**

Outline

- Research integrity: terms and definitions
- Research on research integrity: evolving landscape
- Framework for thinking about human research ethics and research integrity
- US research integrity programs: several examples
- International landscape
- Summary

Terms and definitions

- **Responsible conduct of research (RCR)**
- **Research integrity includes addressing two levels or types of behavior: research misconduct versus detrimental research practices**
- **Research misconduct—US definition:**
  - **Falsification, Fabrication, Plagiarism**
  - **Subject to statutes, debarment from research funding;**
  - **Regulated at the national level in the US and in a number of other countries**

US federal policy on research misconduct:

Definition. The OSTP Policy defines "research misconduct" as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

To be considered research misconduct, actions must:

- represent a "significant departure from accepted practices";
- have been "committed intentionally, or knowingly, or recklessly";
- and be "proven by a preponderance of evidence.

Detrimental research practices

also called questionable research practices

Defining and addressing detrimental research practices: an evolving area in scientific and medical research

Examples:

- **Certain authorship practices** (for example honorary authorship, denying authorship unfairly)
- **Using incomplete data sets**
- **Misleading statistical analyses**
- **Conflicts of interest**
- **Neglectful or exploitative supervision in research**

Detrimental research practices are governed by professional standards

- Professional standards: institutional oversight, journal practices, etc.
  - For example, journal policies on defining and stating authorship contributions
- **Detrimental research practices are more prevalent and arguably more damaging to science than legally defined scientific misconduct**
- Some DRPs lead to skewed findings, introducing bias and distortion;
- Potential to influence social structure of research, discourage junior investigators, provide disincentives for good behavior;

Detrimental research practices: a spectrum

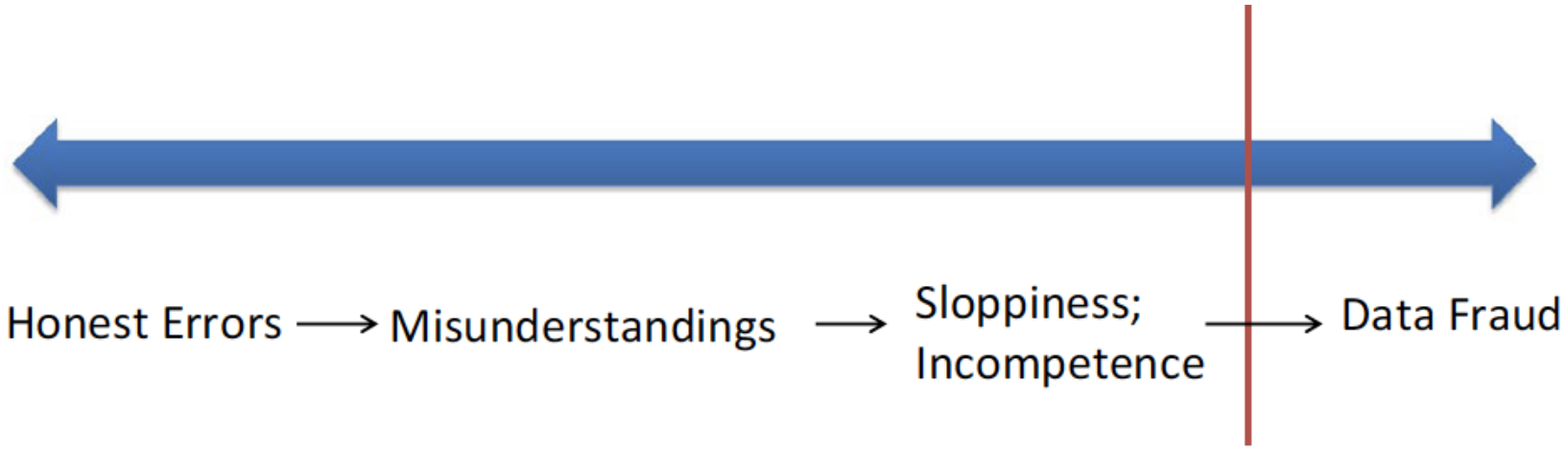


Fig. 1 Spectrum of sources of data errors in clinical trials

***Figure from George, S. L. (2016). Research misconduct and data fraud in clinical trials: prevalence and causal factors. *International journal of clinical oncology*, *21*(1), 15-21.**

Detrimental research practices--selective reporting of clinical trials

In the past, many clinical trials that produced negative findings were not reported in peer reviewed literature

- Intervention being tested failed to produce positive effect, or failed to be superior to comparator

Trials with positive findings were reported

Systematic reviews or meta-analyses of trials would then produce a skewed result;

Currently there is widespread consensus that clinical trial registration is necessary to counteract this problem

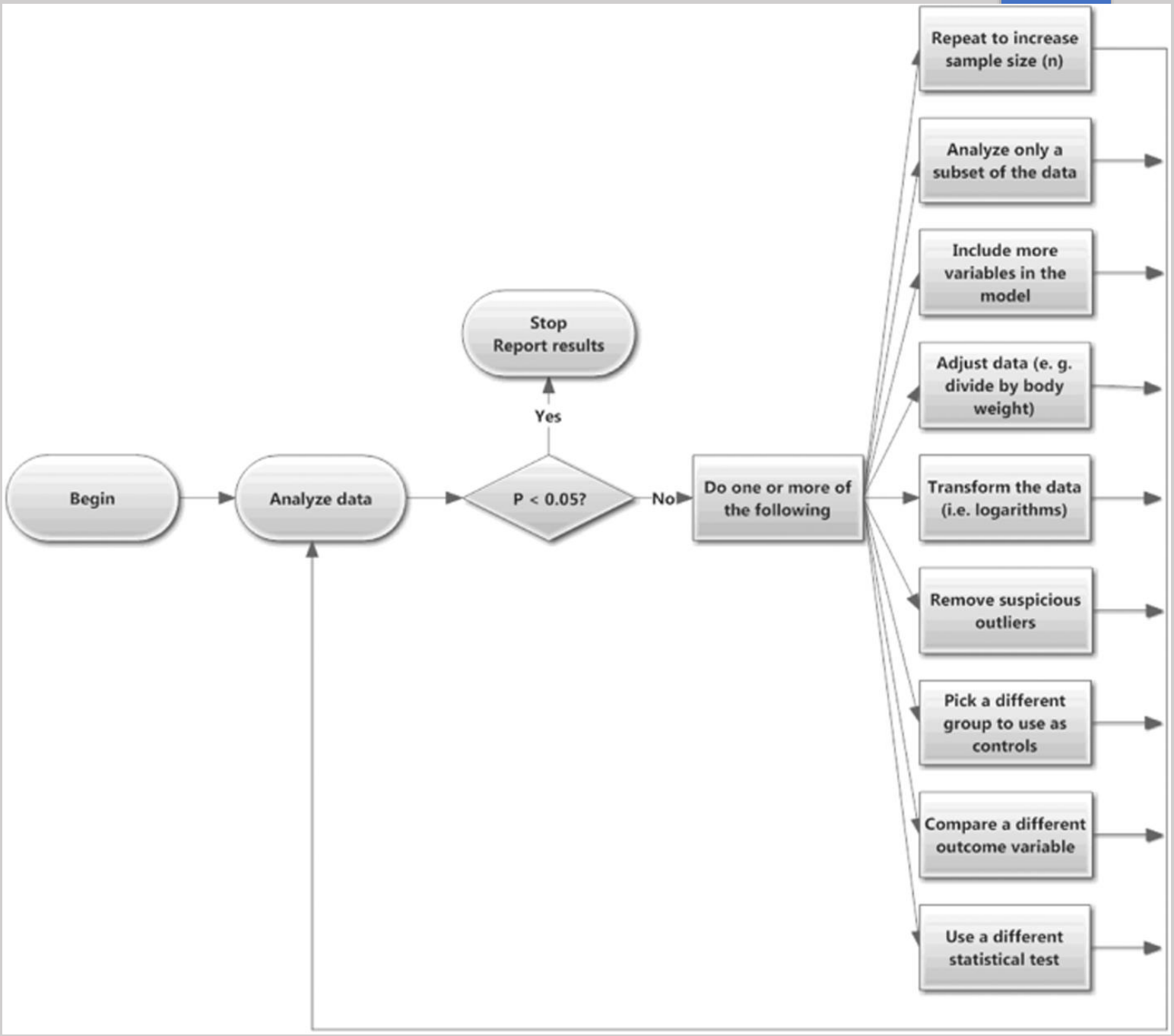
Detrimental research practices can lead to bias--example

P-hacking:

Continuing to mine the data one has collected in the attempt to find a statistically significant result—when the primary statistical analysis shows no statistically significant effect.

The multiple forms of P-hacking

Motulsky, Harvey J. "Common misconceptions about data analysis and statistics." *British journal of pharmacology* 172.8 (2015): 2126-2132.



Some current research on research integrity

In prior decades, scientists believed that science is self-regulating;

- Investigators believed in the "bad apple" theory; that a few bad actors are responsible for violations;

Recent research: misconduct is persistent problem; detrimental research practices are quite common

Estimates of prevalence in the US:

- 1-2% of researchers commit misconduct
- 10% of researchers engage in detrimental research practices;
- Problem: inherently difficult to measure concealed behavior

Research in psychology and behavioral economics

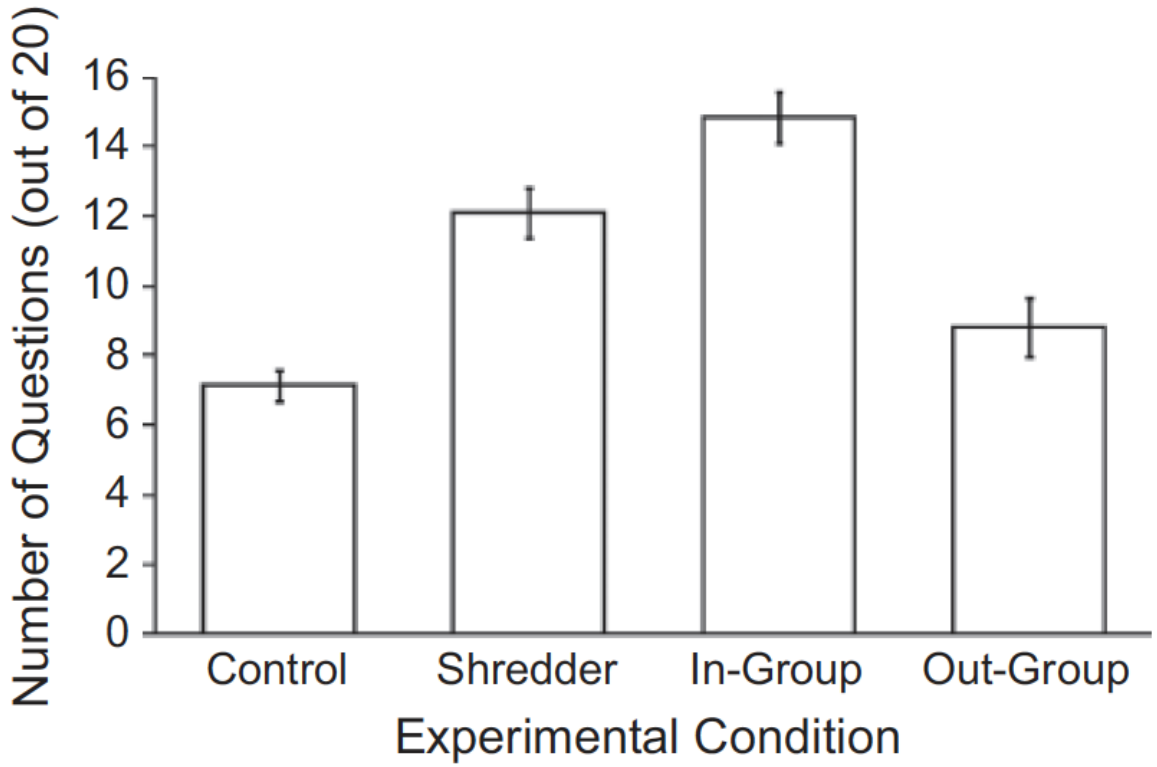
- **A large percentage of people will engage in minor dishonesty and cheating regularly**
- **The social environment, pressures, constraints, and expectations affect this behavior**

Geno, Ayal and Ariely: *Contagion and differentiation in unethical behavior*

Researchers conducted experiments on cheating when students were paid to perform tasks

- **Students are randomly assigned to four groups**
- **All four groups take a quiz under time constraints, receive prorated payments depending on number of correct answers reported**
  - **Group 1: control; test administrator checks answers;**
  - **Group 2: no checking of answers, answers are put into "shredder"**
  - **Group 3: same as Group 2 but with an in-group confederate who cheats**
  - **Group 4: same as Group 2 but with an out-group confederate who cheats**

Results of experiment: number of problems reported as correct varies by condition



Reference: Gino, Shahar Ayal, and Ariely. "Contagion and differentiation in unethical behavior: The effect of one bad apple on the barrel." *Psychological science* 20.3 (2009): 393-398.

Scientists are like other humans

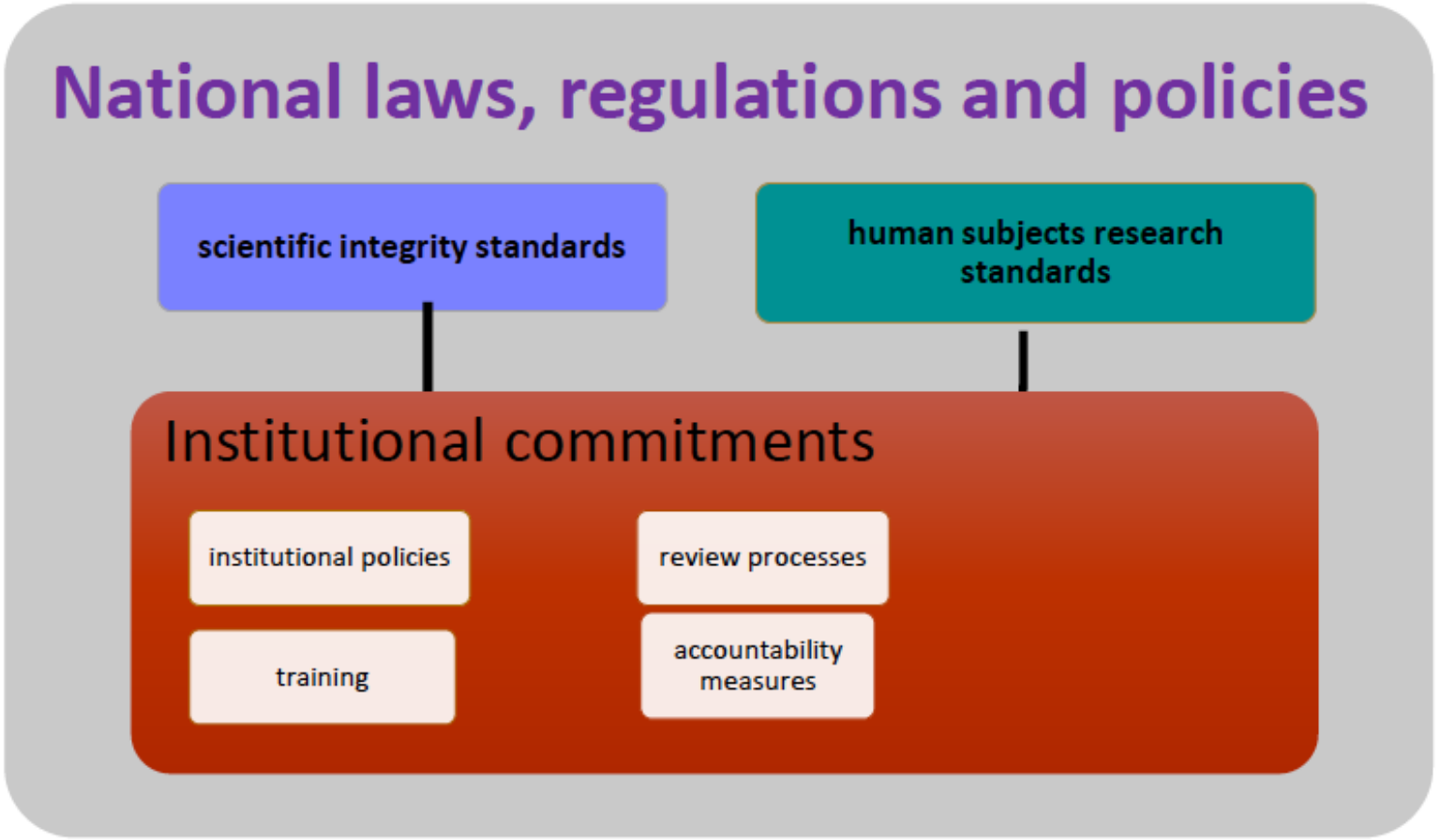
"Why does research misconduct happen? The answer that researchers love is 'pressure to publish', but my preferred answer is 'Why wouldn't it happen?' All human activity is associated with misconduct. Indeed, misconduct may be easier for scientists because the system operates on trust. Plus scientists may have been victims of their own rhetoric: they have fooled themselves that science is a wholly objective enterprise unsullied by the usual human subjectivity and imperfections. It is not. It is a human activity."

Reference: Smith R (2006) Research misconduct: the poisoning of the well. J R Soc Med 99(5):232–237. doi:10.1258/jrsm.99.5.232

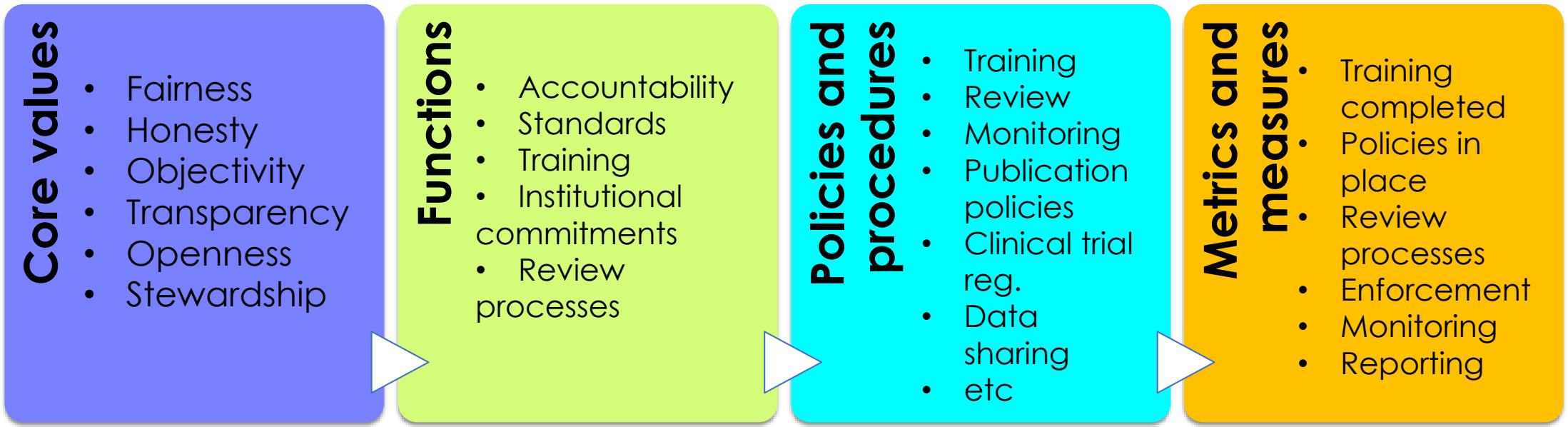
Implications for responsible conduct of research

- Systematic, regular checks and balances are needed
- The social environment and expectations of peers are influential
- Institutions need to create these systems with regular consistent oversight and supportive culture for responsible research

Integrating scientific integrity standards with human subjects research standards



Framework for integrating research ethics and research integrity



Core values

Core values for all scientific research:

- Objectivity
- Honesty
- Openness
- Accountability
- Fairness
- Stewardship

Core values for human subjects research:

- Protection from risks
- Fair distribution of benefits, risks, and burdens
- Respect
- Social value

Functions of the combined research integrity and research ethics system

National level

- Standards: national laws, standards, policies
- Accountability: enforcement, monitoring, transparency

Institutional level

- Institutional policies
- Training
- Review processes
- Accountability: enforcement, monitoring, transparency

Policies and procedures—sample list

- Policies on training on RCR and research ethics for researchers (both national and institutional)
- Institutional policies on monitoring and compliance with RCR and ethics standards
- Ethical and scientific review processes
- Registration of clinical trials
- Publication policies
- Conflict of interest policies

Metrics

Measurement challenges

- **No "gold standard"** measurement of effectiveness of RCR programs
- **Difficult to measure impact** on misconduct or detrimental practices—reticence to report
- **Surveillance bias:** increased vigilance may lead to increased detection—not necessarily increased incidence of problems

Procedural measures may be useful (e.g. % completion)

- **Training completed**
- **Policies in place** (national, institutional)
- **Enforcement mechanisms defined**
- **Registration of clinical trials**
- **Journal publication policies**
- **Conflict of interest standards in place**

Different levels and types of oversight: examples from US system

National standards, laws, policies

Institutional policies and procedures

Investigator practices

US national level oversight and enforcement

Department of Health and Human Services (DHHS) Office of Research Integrity (ORI)

ORI oversees NIH-funded and conducted research

ORI handles allegations of misconduct per federal regulations (serious misconduct)

Conducts investigations, issues findings

National Science Foundation Office of Inspector General (NSF-OIG)

Oversees NSF funded research

Office of Research Integrity

- Extensive resources and training materials,
- Promotes education on responsible conduct of research
- Handles investigation of allegation of misconduct (legal definition)
- Misconduct investigations result in legal determination regarding misconduct and public disclosure of findings
- Investigators might be barred from receiving research funding for certain period

NIH: extramural versus intramural

Extramural: NIH as funder/sponsor of research

Research integrity policies apply to grants to institutions

- Mandated RCR training in all training grants

Additional policies related to detrimental research practices

- Focus on reproducibility in science, conflicts of interest, clinical trial registration, etc.

NIH: extramural versus intramural

Intramural: NIH as an institution conducting research Research integrity policies apply to NIH intramural investigators and scientific staff

- NIH conducts training for all investigators and trainees
- Policies and SOPs regarding responsible conduct
- Attendance at annual case studies series required for all research groups
- Extensive training resources available for individual program needs

NIH intramural program oversight

Education of scientific staff and oversight of laboratories and research programs conducted in NIH intramural program

- Similar to level and type of oversight needed at academic institutions
- Addresses research integrity education and prevention of both serious misconduct and detrimental research practices

NIH intramural program, cont'd

Critical role of Laboratory Head/Principal Investigator

- Routine review of primary data
- Education on research integrity and good scientific standards
- Maintaining "open door" policy regarding discussion of concerns amongst junior investigators and trainees

Two most common mistakes at the level of the lab or research group:

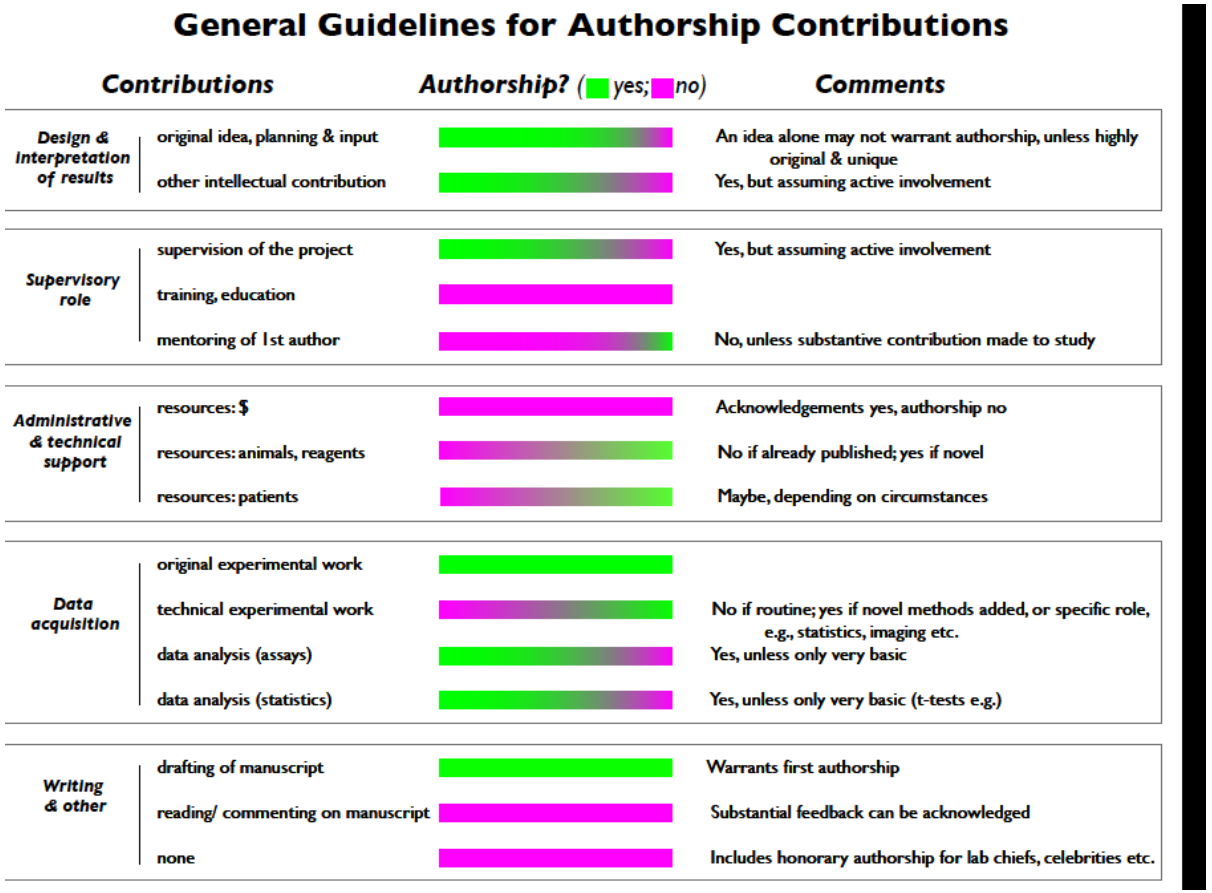
- Assuming people know the best practices without training or stating policies explicitly
- Allowing scientists to work in isolation

Guidance for NIH intramural program supervisors:

Promoting research integrity

Example of NIH intramural program policies to address/prevent detrimental research practices

Guidelines for authorship contributions



General Guidelines for Authorship Contributions

Contributions		Authorship? (yes; no)	Comments
Design & interpretation of results	original idea, planning & input		An idea alone may not warrant authorship, unless highly original & unique
	other intellectual contribution		Yes, but assuming active involvement
Supervisory role	supervision of the project		Yes, but assuming active involvement
	training, education		
	mentoring of 1st author		No, unless substantive contribution made to study
Administrative & technical support	resources: $		Acknowledgements yes, authorship no
	resources: animals, reagents		No if already published; yes if novel
	resources: patients		Maybe, depending on circumstances
Data acquisition	original experimental work		
	technical experimental work		No if routine; yes if novel methods added, or specific role, e.g., statistics, imaging etc.
	data analysis (assays)		Yes, unless only very basic
	data analysis (statistics)		Yes, unless only very basic (t-tests e.g.)
Writing & other	drafting of manuscript		Warrants first authorship
	reading/ commenting on manuscript		Substantial feedback can be acknowledged
	none		Includes honorary authorship for lab chiefs, celebrities etc.

Authorship dispute resolution

Processes for Authorship Dispute Resolution

In cases of authorship disputes related to composition and/or order of authors, in which only NIH authors are part of the dispute, the Deputy Director for Intramural Research (DDIR) encourages parties to engage in direct dialogue (#1 below) to resolve matters. Use of a "pre-nuptial agreement" for collaborations is strongly suggested. The other processes (#s 2-4) described below are also available for resolution. All these processes should be handled as expeditiously as possible.

1. **Direct Dialogue**
   This involves the parties to the dispute discussing their perspectives and working to reach an agreeable resolution based on the Guidelines for the Conduct of Research in the Intramural Research Program at NIH.
2. **Mediation**
   Parties to a conflict may choose to work with the Office of the Ombudsman to participate in a confidential mediation process to assist in finding resolution to authorship disputes. The Office has a pool of senior NIH scientists who can serve as co-mediators. The Ombudsman mediators do not advocate for any particular outcome and remain a neutral third-party assisting with the exploration of perspectives, rationales, and options. The parties themselves decide on the terms of any agreement.
3. **Peer Panel**
   Parties to an authorship dispute would agree to present their perspectives to a panel of three NIH scientists with scientific expertise in the area of research, no conflict of interest, and, when possible, with no affiliation with the ICs of the involved authors. By entering into the voluntary Peer Panel process, the parties involved would agree in writing to accept and abide by the decision of the panel. The parties would further agree that in abiding by the decision, they will not dispute this issue at the level of the journal's editors or other public forum. Further description of this proposed process can be found below.

Additional NIH intramural training and guidance

- Guidelines for scientific record keeping
- A guide to training and mentoring
- Collaborative research
- Authorship
- Peer review
- Social responsibility
- Conflict of interest

International perspectives on research integrity

- Few studies of research integrity issues
- **Data available indicate similar issues in countries in other regions (Europe, Asia, Latin America)**
- Some differences in types of detrimental research practices that are more prevalent;
  - For example, in some countries plagiarism is more common
- **World Congress on Research Integrity**: growing international discourse to address problems, share resources, and develop international standards

Summary

- Responsible conduct of research is increasingly recognized as an area needing consistent policies and proactive approach
- Science is not self regulating, and both national and institutional policies and oversight are needed
- Misconduct defined as fraud, fabrication, or plagiarism is relatively rare; detrimental research practices are common and possibly more damaging
- More empirical research on effective approaches to RCR is needed

Acknowledgements

- **Patrica Valdez**, NIH extramural Research Integrity Officer
- **Melissa Colbert**, Director of Research Integrity and NIH Agency Intramural Research Integrity Officer
- **Carla Saenz**, Regional Bioethics Advisor, PAHO
- **Pat Weitzel**, Director of the Office of Research Integrity at Houston Methodist Research Institute

Selected resources

- **DHHS Office of research integrity resources:** https://ori.hhs.gov/general-resources-0
- **NIH resources for training directors:** https://oir.nih.gov/sourcebook/ethical-conduct/responsible-conduct-research-training/resources-training-directors
- **NIH case studies in responsible conduct of research, used for training purposes:** https://oir.nih.gov/sourcebook/ethical-conduct/responsible-conduct-research-training/annual-review-ethics-case-studies/research-cases-use-nih-community#theme18

Resources cont'd

- **NIH Guide: Update on the requirement for instruction in the responsible conduct of research**; https://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-019.html
- **European code of conduct for research integrity** http://www.allea.org/wp-content/uploads/2017/05/ALLEA-European-Code-of-Conduct-for-Research-Integrity-2017.pdf
- **Singapore Statement on research integrity** Available at: www.singaporestatement.org
- **National Academies Report, Fostering Research Integrity**; https://www.nap.edu/catalog/21896/fostering-integrity-in-research
- **World Conferences on Research Integrity;** https://wcrif.org/