Responsible Conduct in Biomedical Research

BIO 664

Meet and Greet

- Introduce yourselves.
- Draw a diagram on the sheet or paper- a representation of the group's interests and expectations (10 mins)
- 1 person per group introduces the group

Responsible Conduct of Research

Planning

- Protection of research subjects (human and non-human)
- Conflicts of interest (financial, commitment, personal and intellectual)

Conducting

- Data collection, management and storage, sharing, and ownership
- Mentorship
- Collaborative research

Reporting and Reviewing

- Authorship and publication practices
- Peer review

https://ori.hhs.gov/sites/default/files/rcrintro.pdf

Syllabus

	19 September 2018	**26 September 2018**
9:00 – 10:00	Meet and Greet Introduction to course: content, expectations Overview of Ethics	Intellectual Property, Patents, and Technology Transfer
10:15 – 11:45	Video: THE LAB Authorship and the reviewer process Confidentiality Misconduct Whistle-blowing	Group Presentations
11:45 – 13:15	LUNCH (choose topic for group presentations)	LUNCH
13:15 – 15:00	Record Keeping Mentoring Collaboration Competition, Conflict of Interest	Group Presentations
15:15 – 17:00	Introduction to the Protection of Human Subjects	
	Group Presentation Preparation – Choosing topics	Summary Course feedback survey

Course Design and Aims

- To prepare you to recognize the ethical dilemmas and scenarios facing every scientist
- Familiarize ourselves with the written codes that govern scientific behavior
- Provide you with skills to identify issues and evidence related to a specific problem
- Give you the resources and guidelines for ethical decision-making

Morals vs Ethics

Morals	**Ethics (applied)**
Values that emanate from our inner convictions and judgment	Application of moral values into a system of analysis to determine concepts of good or bad behavior
Principles of right versus wrong	Right versus wrong conduct
Set by individual or group	Depends on specific situation

Why do we need ethics?

In general “professions” require a system of ethics due to the **complexity** or specialization of the field and the need for expertise to make an **informed** decision

- Medicine (“first, do no harm”)
- Lawyers (respect of client confidences)
- Engineers (safety of public)
- Law Enforcement (use of force)
- Business (financial fraud)

Image: https://www.sophia.org/online-courses/introduction-to-ethics

Why do scientists need ethics?

- Promotes **aims of research**
- Promotes values essential to **collaborative** work
- Ensures researchers can be **held accountable** to the public and helps **build public support** for research
- Promotes important **moral and social values**

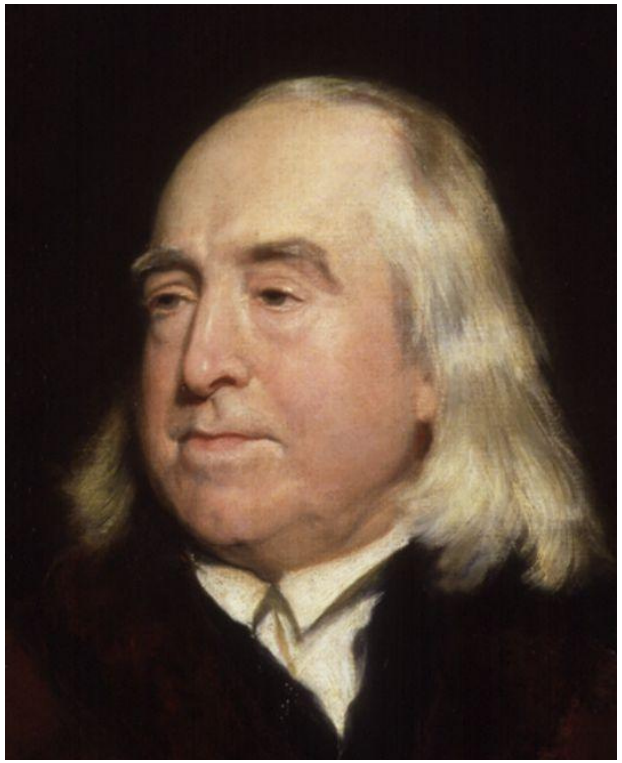
https://www.niehs.nih.gov/research/resources/bioethics/whatis/

Ethics as a "science"
Ethical Theories

- Need to be internally consistent
- Must be useful for decision making
- Must be rational (agree with our general moral intuition)

Ethical theories: two major categories

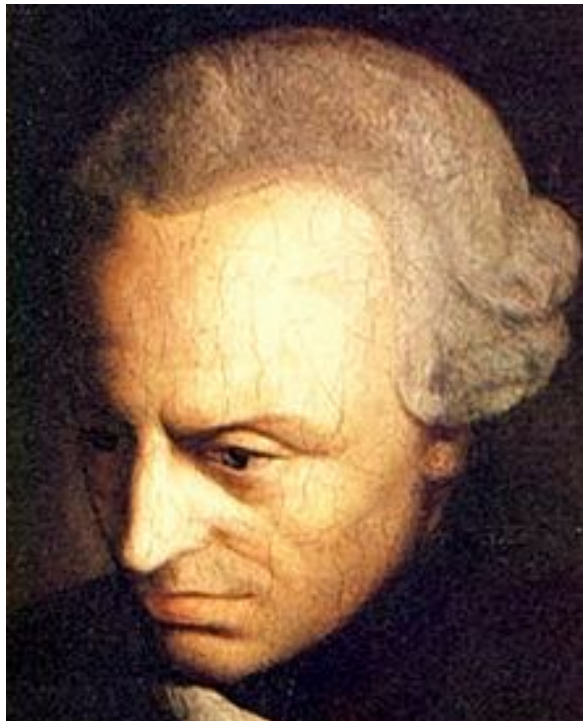
Teleological



telos – end or purpose

Jeremy Bentham

Deontological



deontos – that which is binding, right, proper

Immanuel Kant

Images:

Ethical theories: two major categories

Teleological

(Bentham): "it is the greatest happiness of the greatest number that is the measure of right and wrong"

Able to sacrifice the well-being of someone if it brings benefits to a greater number of people.

Also known as: Consequentialism, utilitarianism

Deontological

Emphasis on *universal imperatives* (Kant):

> the rightness or wrongness of an act from the *character of the act* itself rather than the outcomes of the action

Ignores the consequences (harm) that might occur if we do the right thing.

Is lying wrong?

Ethical theories: two major categories

Teleological

Who is affected by that decision? How are these persons affected? Is this effect strong or weak? Is it in the near future or far away?

Deontological

Can I turn this into a rule for everyone?

Both approaches are imperfect but useful as tools

Ethical blindness and unethical decisions

Why do good people do bad things?

Decision making is "less rational and deliberate but more intuitive and automatic"[1]

- Inappropriate perceptions of reality
- Making decisions based on personal interpretation of the reality
- If this interpretation becomes too narrow, the ethical aspects of a decision might not be taken into account.
- People can become ethically blind: temporary inability to see ethical dilemma

[1]Palazzo et al. (2012)

https://www.coursera.org/learn/unethical-decision-making/home/welcome

Ethical Decision-Making Model

The influence of moral intensity factors

Magnitude of Consequences
Temporal Immediacy
Social Consensus
Proximity
Probability of Effect
Concentration of Effect

Carrying out the decision
despite opposition or possible consequences

I act

Moral ACTION

Decide what to do
Is there support or lack of support by peers?

I think I will

Moral INTENTION

Weighing what to do
What is the harm or benefit of my action? How likely are they to actually occur?

I ask

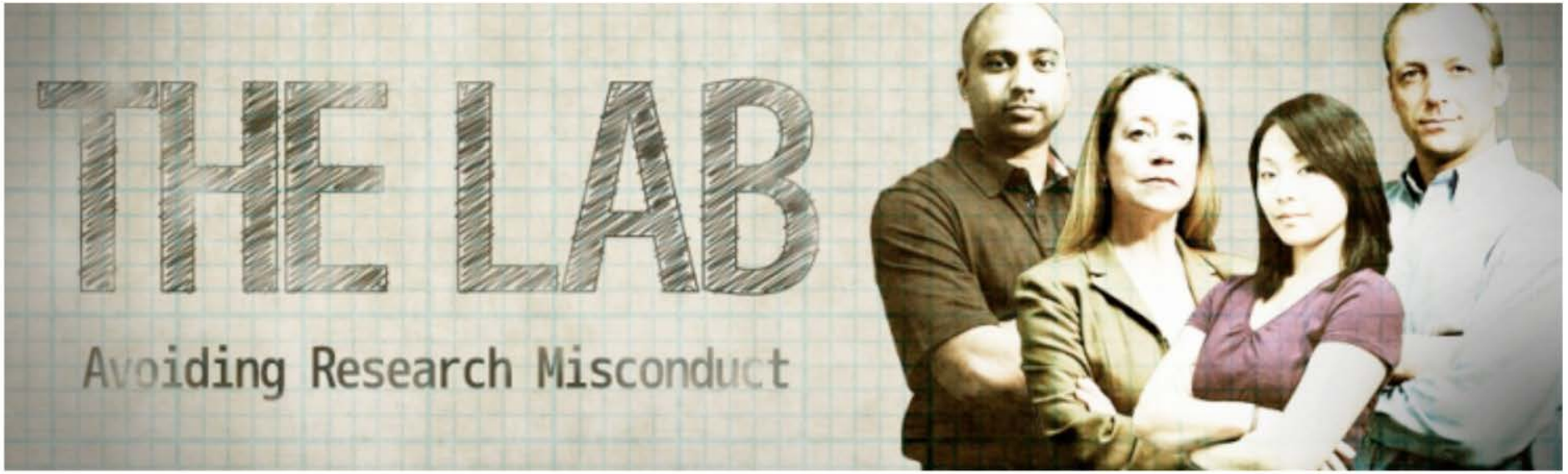
Moral JUDGMENT

The gut feeling
What does my social group think is right or wrong? How close am I to the people affected?

I feel

Moral AWARENESS

Rest (1986), Jones (1991)



https://ori.hhs.gov/thelab

Who should be an author: First, last, corresponding?

a. YOU: Ph.D. student who ran the experiments, analyzed data, wrote draft

b. post-doc who trained you when you started in the lab

c. collaborator who gave you advice on additional control experiments

d. collaborator who gave you a plasmid that you needed to do the experiments

e. your PhD thesis advisor who is not the PI of the lab, but a senior group leader, who came up with the idea for the research, helped design and guide the experiments, and who also helped to write the paper

f. PI of the lab, who gets funds from EPFL from which ultimately funds your work

g. a rotation student who designed a better image analysis code that you used

h. a histologist who sectioned and stained hundreds of slides that you analyzed

i. graduate student who left without a publication, but spent 2 years establishing the initial experiments

Authorship: a public responsibility

Criteria:

1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Provide approval for publication of the content
4. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

International Committee of Medical Journal Editors (ICMJE) guidelines

Authorship: a public responsibility

Acknowledgements: contributors who do not meet these criteria but provided important contributions

Large, multi-center group:

1. Identify the individuals who accept direct responsibility for the manuscript
2. Should clearly identify all individual authors as well as the group name

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship

Plagiarism = misconduct

Authorship and You

How did you become an author on a scientific paper?

Who decided who should be an author?

Who decided the order of authorship?

Do you have an agreement with your PI regarding authorship rules?

Potential conflicts of interest in academic publications

Related to:

- Individual Authors' Commitments
- Project Support
- Commitments of Editors, Journal Staff, or Reviewers

And other issues:

- Negative Data
- Publication Bias
- Corrections, Retractions, and “expression of concern”
- Copyright
- Open Access

Peer Review

- Peer review: (typically anonymous) review of manuscript by other experts in a similar field before publication
- What are the pros? Cons?
- Peer review vs community decision on scientific value
- Peer reviewer anonymity? Author anonymity to reviewer?

Peer Review

- Responsibilities of the reviewer:
  - Responsiveness
  - Competence
  - Impartiality
  - Confidentiality
  - Constructive criticism
  - Responsibility to science
- Is it ever appropriate for a peer reviewer:
  - to give a paper to a graduate student for review?
  - to use ideas from an article under review to stop unfruitful research in the reviewer's laboratory?
  - to use ideas from a paper under review, even if the reviewer's method to achieve a result is different from that used in the paper under review?

Lack of Peer Review

A fake paper with multiple flaws was sent to several (open-access) journals.

- Of the 106 journals that performed any review, 70% accepted the paper.
- Of the 304 submissions, only 36 had reviewer comments that recognized the paper's scientific flaws

Bohannon, J. Who's Afraid of Peer Review? Science, 2013.

Randall Munroe

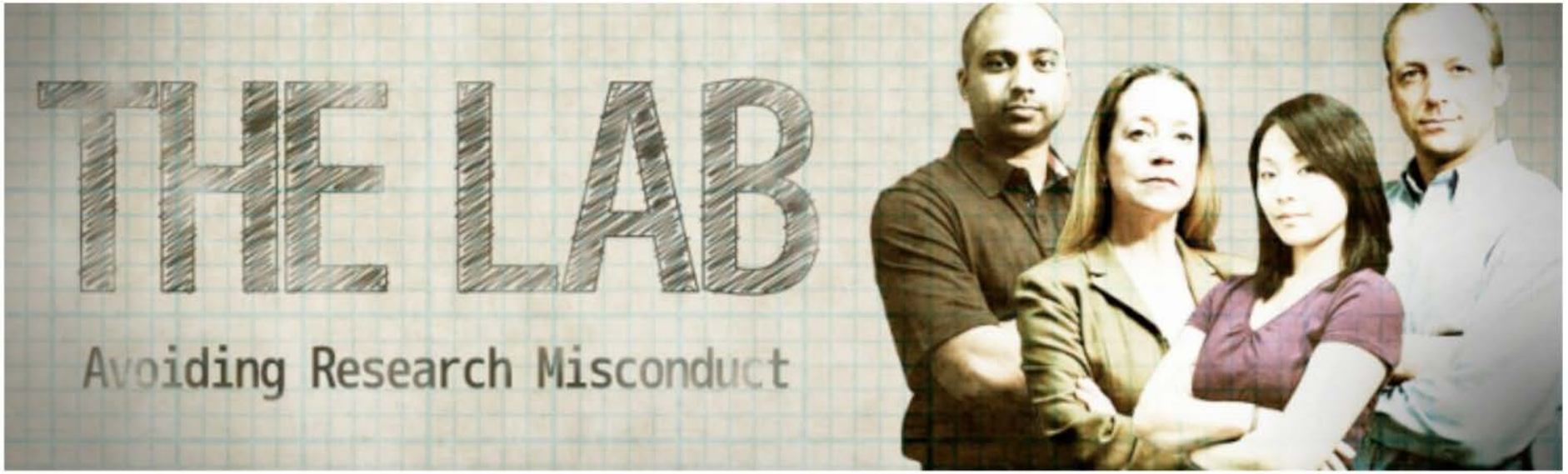
Peer Review and Misconduct

- Why? Motivations.
- Who performed the misconduct?
- Who is responsible for the misconduct?
  - Where did the data come from?
  - Were publications or reviewers not critical enough? Do they hold any responsibility in publishing the fraudulent papers?
  - What are the (larger) consequences?

Peer Review Resources

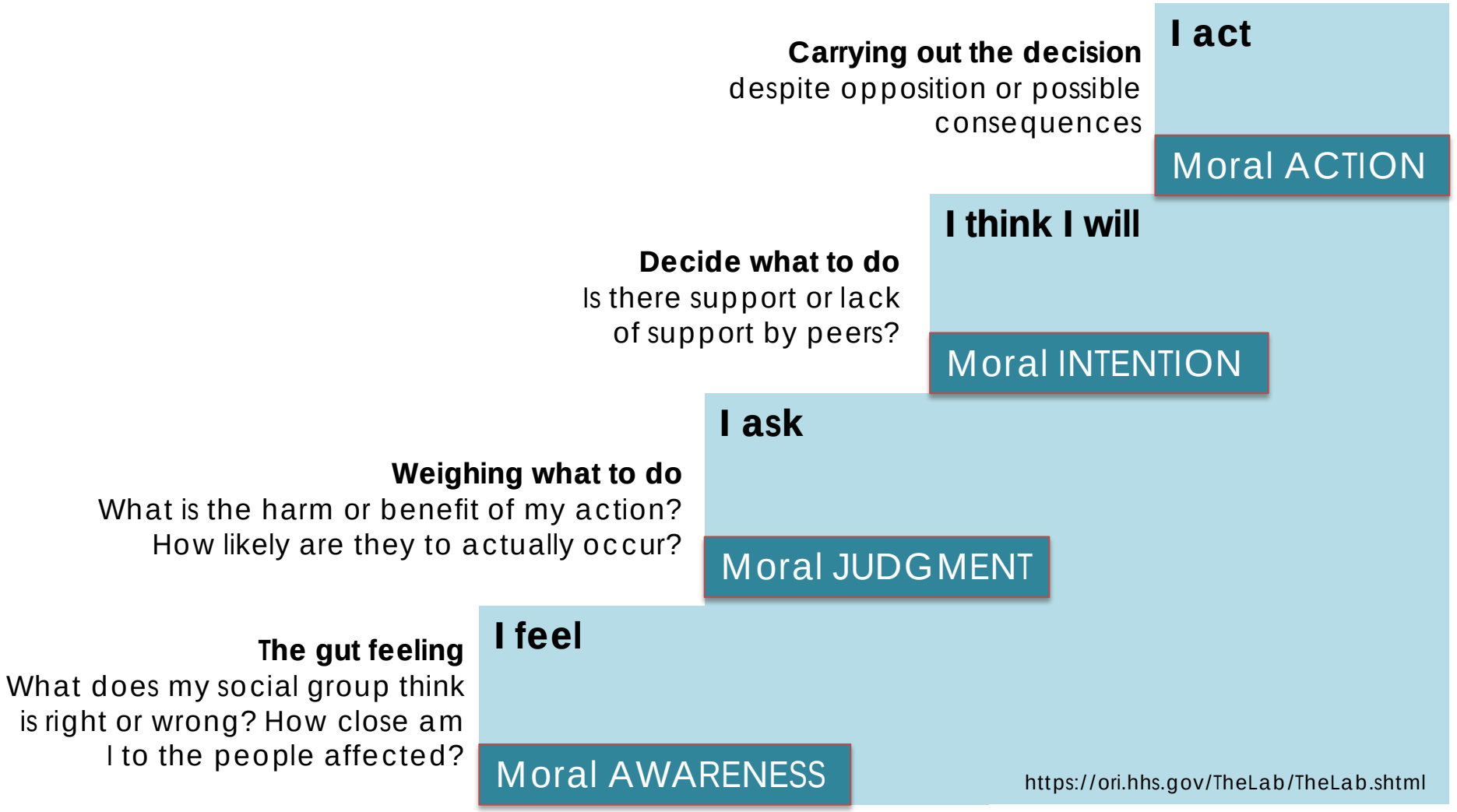
Nature Master Class on Peer Review

https://masterclasses.nature.com/courses/205



https://ori.hhs.gov/thelab

Ethical Decision-Making Model



People can react based on different moral intensity factors

- How much a particular social group (colleagues, friends, family) agrees that a given action is good/ bad and what they will think about you
- How close or distant you feel to the people affected by your decision
- How much your actions harm or benefit someone
- How likely it is that something bad will happen as a consequence

Do nothing vs. Whistle-blowing? Preventing the negative consequences is a positive in the long-run.

Whistleblowing procedures @ EPFL

Whistleblower: someone who reveals or tries to reveal information concerning legally or ethically incorrect behaviour, of which he/she has obtained knowledge in the course of his/her activity within EPFL.

Objective:

- To implement a whistleblowing procedure and mechanism for reporting of serious misconduct within or relating to EPFL
- To protect the whistleblower
- To avoid the creation of an incriminatory atmosphere at EPFL that would be detrimental to the working environment.

From http://research-office.epfl.ch/research-ethics-integrity/research-misconduct/whistleblowing-procedure

Whistleblowing procedures @ EPFL

Serious misconduct may occur in the form of:

- legally or ethically incorrect behaviour on the part of EPFL members within the framework of their activities at EPFL;
- scientific misconduct, undeclared conflicts of interest;
- failure to respect legal or supervisory obligations;
- abusive use of financial resources and installations;
- failure to respect or circumvention of internal directives and control mechanisms.

To file a complaint: Submit a report to the EPFL ombudsperson:

Prof. Patrick Francioli

Commission cantonale d'éthique de la recherche sur l'être humain

Avenue de Chailly 23, CH-1012 Lausanne

Tél. +41 21 316 18 30/31, Email : patrick.francioli@vd.ch

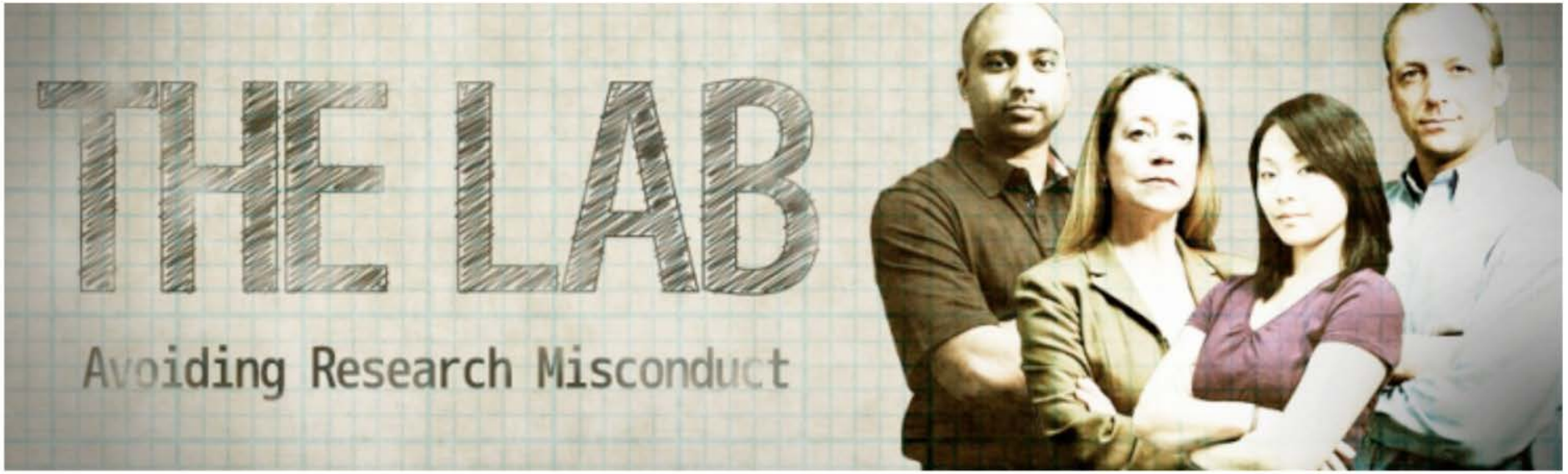
From http://research-office.epfl.ch/research-ethics-integrity/research-misconduct/whistleblowing-procedure

Dealing with errors

- **Erratum**: correction of errors introduced to the article by the publisher
- **Corrigendum:** changes to the published article that the authors wish to make
- **Retraction**: notification of invalid results due to pervasive error or unsubstantiated or irreproducible data

Erratums, corrections, and corrigendums are equivalent for some publishers

https://www.nature.com/authors/policies/corrections.html
https://www.nlm.nih.gov/pubs/factsheets/errata.html
https://www.elsevier.com/editors/perk/policy-and-best-practice-errata-And-corrigenda



https://ori.hhs.gov/thelab

Why do we need mentors?

- **Professional development** (time management, conflict resolution, project planning, grant writing, basic organizational and management skills)
- **Access to opportunities and networks** (research collaborations, funding, etc.)
- **Emotional support** (to deal with the stress and pressure of the tenure track and life in a new location)
- **A sense of community** (both intellectual and social)
- **Accountability** (for research and writing)
- **Institutional/political sponsorship** (someone to advocate their best interest behind closed doors)
- **Role models** (who are navigating the academy/industry in a way they aspire to)
- **Safe space** (to discuss and process their experiences without being invalidated, questioned, devalued and/or disrespected)

Responsibilities of the trainee

- Identify career plans
- Locate prospective mentors
- Distinguish between supervisors and mentors
- Be clear about needs and expectations
- Keep learning about effective mentoring

https://phd.epfl.ch/EDBB_Internal_Regulations

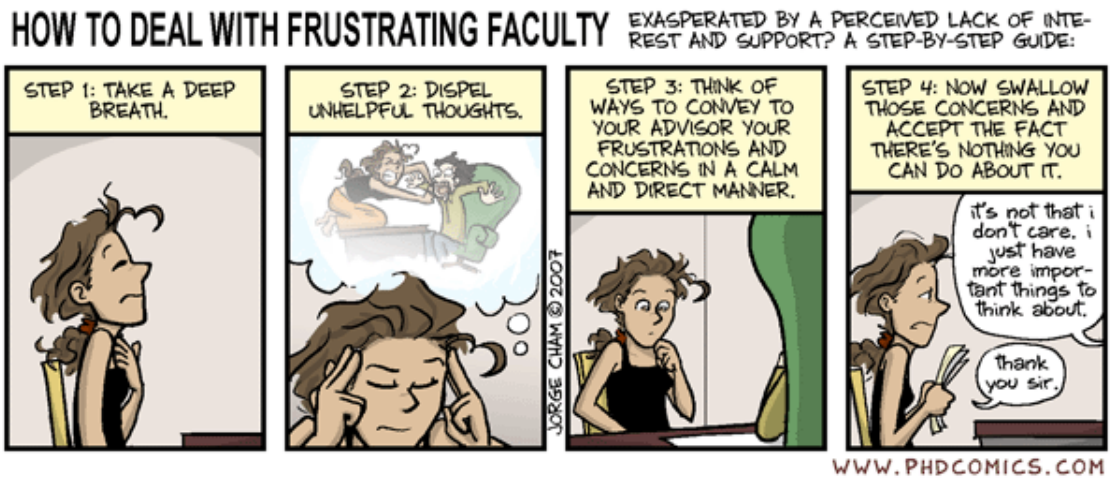


Image from *Piled Higher and Deeper* by Jorge Cham, http://www.phdcomics.com/comics/archive.php?comicid=892

Mentorship

1. What can be done to understand mentoring better? What quantitative and/or qualitative studies might be undertaken?

2. Mentoring is a highly useful tool. How can it be made a higher priority in your institution? What guidelines or programs are in place to promote mentoring in your lab/department/school/institution?

3. If a trainee believes that he or she has been seriously injured by something a mentor has done, how can the trainee seek redress? How should he or she proceed?

4. To what extent is empathy necessary on the part of the mentor? What about cultural or other differences when they interfere with understanding?

Data Analysis and Record Keeping

- Why keep a lab notebook?

- What do you write?

Data Analysis and Record Keeping

- Should Millikan be judged for his scientific ethics given that he
  - was a highly successful scientist?
  - got the right answer?
- If Millikan had not claimed to have published all the data, would he still be guilty of questionable behaviour?
- When does a scientist uses "intuition" as criteria?
- Which is worse: intentional manipulation of data or outright fabrication of data?

Data Analysis and Record Keeping

- Can sloppy/bad record keeping be considered as misconduct?
- Is it ok to "tweak" data for a grant application since no one will really hold you to it? Why or why not?
- Is it legally necessary to have records of data: for a grant application? For a manuscript? For a published meeting abstract? For presentation at a lab meeting? How much data / recordkeeping is necessary?
- If you publish a paper and others question the findings, can 'authorities' look in your lab notebook? If your data isn't there, is that "proof" that you fabricated data?

Record Keeping: the lab notebook is a legal document

- Why?
  - EPFL owns your data and notebooks (intellectual property) -> must rest on campus
  - Reproducibility
  - Longitudinal memory/ scientific legacy
  - Used to verify results in fraud and other legal cases
- Ethics
  - All data and analysis go into the notebook – including outliers, failed experiments
  - No pages come out of the notebook
    - Do not erase, but only strike out the contents
    - Use a permanent writing utensil (no pencil)
    - Do not skip pages (cross out unused pages)
- A guideline: Guidelines for Scientific Record Keeping in the Intramural Research Program at the NIH

Good Experimental Design and Analysis is fundamental to reproducibility

The ethics: Money spent on irreproducible preclinical research exceeds 50%, or approximately US$28B/year (PlosBiology 2015, Freedman et al.).

Proposed Solutions:

- Good record keeping
- Learn good experimental design
  - Continuing courses in animal experimentation
  - EPFL and UNIL courses
- Learn the best practice in statistics and data analysis
  - EPFL and UNIL courses
  - e.g. learn R

Human Subjects in Research

Definition of Research

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

U.S. Federal Guidelines 45 CFR 46.102(d)

Definition of a Human Subject

A living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information.

U.S. Federal Guidelines 45 CFR 46.102(f)

Human Subject Data

- **Intervention:**
  - physical procedures (e.g. venipuncture)
  - manipulations of the subject or the subject's environment
- **Interaction**: communication or interpersonal contact

United States Federal Guidelines (32 CFR 219.102.f)

National Archives and Records Administration (ARC 824608)

Human Subject Data

- **Identifiable private information**
  - information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place
  - information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g. a medical record)

www.healthandwellnesscare.com

United States Federal Guidelines (32 CFR 219.102.f)

Recent Historical Background

- WWII – Nazi and Japanese vivisection and other medical experimentation

Nuremberg Code (1947)

Declaration of Helsinki (1964)

Institutional Review Boards (1975)

- Tuskegee Syphilis Study (1932-1972)

Belmont Report (1979)

Belmont Principles

Nuremburg Code

1. Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.
2. The experiment should aim at positive results for society that cannot be procured in some other way.
3. It should be based on previous knowledge (like, an expectation derived from animal experiments) that justifies the experiment.
4. The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.
5. It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.
6. The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.
7. Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.
8. The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.
9. The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.
10. Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous

The Basic Principles of Human Research

1. **Autonomy – voluntary informed consent** information, comprehension and voluntariness

2. **Beneficence –** (1) do no harm and (2) maximize possible benefits and minimize possible harms

3. **Justice –** Who ought to receive the benefits of research and bear its burdens? in the sense of ”fairness in distribution” or ”what is deserved.”

Infamous Pre-IRB (1975) Experiments

Tuskegee Syphilis Study (1932-1972):

- Studied untreated syphilis in rural African-American men
- None were told they had syphilis or were treated with penicillin
- Led to 1979 Belmont Report

Milgram Shock Experiment (1961): video

- Studied willingness of participants to obey authority figures despite their personal conscience
- Inflicted emotional stress on participants
- "Teachers" did not know they were not harming their "victims"

Stanford prison experiment (1971)

- Studied how participants would conform to the roles of guard and prisoner
- Prisoners: lack of fully informed consent, were not protected from harm
- Led to mandatory approval by an institutional review board or ethics committee for all studies

Human research at EPFL

Research involving work with humans

All research involving human subjects must be conducted in accordance with **three basic ethical principles**, namely respect for persons, beneficence and justice (*Declaration of Helsinki*). It is generally agreed that these guidelines, which in principle have equal moral force, guide the conscientious preparation of proposals for scientific studies.

Furthermore, research involving human subjects should be carried out only by, or strictly supervised by, suitably **qualified and experienced investigators and in accordance with a protocol** that clearly states: the aim of the research; the reasons for proposing that it involves human subjects; the nature and degree of any known risks to the subjects; the sources from which it is proposed to recruit subjects; and the means proposed for ensuring that subjects will be adequately informed and will voluntarily give their consent (*Informed Consent*). The protocol should be **scientifically and ethically established by one or more suitably constituted review bodies**, independent of the investigators.

Self-Assesment of your research proposal

You can use the **kofam** (Swiss Coordination office for research involving humans) **Wizard** to categorize your research project. The **Wizard** will tell you what **type of research project** it is and which **category** the project or the clinical trial must be allocated to, and which **type of authorization** must be requested.

Presidential Decision	• Use of available biological material and health-related personal data for research, with informed consent • Modification of authorized research projects, if they do not raise specific ethical, scientific or legal issues • Checks if the requirements for the local specificities of multi-center clinical trials are fulfilled

- Research Ethics
  - Research Integrity
  - Research Ethics Assessment
    - Ethical Review
      - Research involving work with humans
        - Invasive research
        - Non-invasive research
        - Clinical Trials
        - Legislation and Guidelines
      - Research involving work with human cells/tissues
      - Research involving work with animals
      - Research involving work with personal data
      - Research that may impact environment & health and safety
      - Research involving work with Developing Countries/Third Countries
      - Research involving work with potential for military applications
      - Research involving work that could be potentially be misused
    - Research Ethics Committees
    - EPFL Human Research Ethics Committee

EPFL Information Sheet for Participants in Research Studies

INFORMATION SHEET FOR PARTICIPANTS IN RESEARCH STUDIES

You will be given a copy of this information sheet.

Project Title: Cliquez ici pour taper du texte.

This study has been approved by the EPFL Research Ethics Committee (HREC No: Cliquez ici pour taper du texte.)

As a participant you have the right to withdraw from the study at any time…

Details of the study:

Cliquez ici pour taper du texte.

What are the risks?

Cliquez ici pour taper du texte.

Please ask us if there is anything that is not clear or if you would like to receive more information.

It is up to you to decide whether you will take part or not; choosing not to take part will not disadvantage you in any way. As a participant you have the right to withdraw from the study at any time without giving a reason or facing negative consequences.

All data will be collected and stored safely and reported in an anonymous form, in accordance

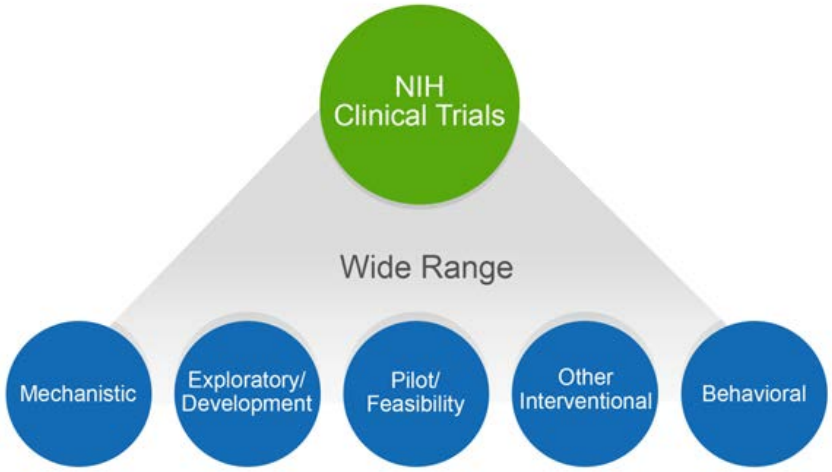
IRB approval needed or not?

- surveys and questionnaires
- interviews and focus groups
- biographies
- analyses of existing data or biological specimens
- classroom exercises solely to fulfill course requirements or to train students in the use of particular methods or devices
- experimental data systematically gathered but not published
- experimental data systematically gathered for a dissertation

http://www.research.uci.edu/compliance/human-research-protections/researchers/activities-irb-review.html

New NIH Clinical Trials Policy

- Expanded definition of "clinical trial"
- Clinical specific funding opportunities
- Additional review criteria
- Expanded reporting in ClinicalTrials.gov
- Training Resources link



https://grants.nih.gov/policy/clinical-trials.htm
https://www.nature.com/collections/ztwxfkgdrv

Case Quinn et al.

VIRAL LOAD AND HETEROSEXUAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

THOMAS C. QUINN, M.D., MARIA J. WAWER, M.D., NELSON SEWANKAMBO, M.B., DAVID SERWADDA, M.B., CHUANJUN LI, M.D., FRED WABWIRE-MANGEN, PH.D., MARY O. MEEHAN, B.S., THOMAS LUTALO, M.A., AND RONALD H. GRAY, M.D., FOR THE RAKAI PROJECT STUDY GROUP

ABSTRACT

Background and Methods We examined the influence of viral load in relation to other risk factors for the heterosexual transmission of human immunodeficiency virus type 1 (HIV-1). In a community-based study of 15,127 persons in a rural district of Uganda, we identified 415 couples in which one partner was HIV-1–positive and one was initially HIV-1–negative and followed them prospectively for up to 30 months. The incidence of HIV-1 infection per 100 person-years among the initially seronegative partners was examined in relation to behavioral and biologic variables.

Results The male partner was HIV-1–positive in 228 couples, and the female partner was HIV-1–positive in 187 couples. Ninety of the 415 initially HIV-1–negative partners seroconverted (incidence, 11.8 per 100 person-years). The rate of male-to-female trans-

IN sub-Saharan Africa, the predominant mode of transmission of human immunodeficiency virus type 1 (HIV-1) is through heterosexual contact, and the rate of transmission by this means is increasing throughout Asia and in many industrialized countries.[1,2] A wide variety of behavioral and biologic risk factors are associated with the risk of transmission, including the frequency[3-5] and types[6] of sexual contact, the use or nonuse of condoms,[5,7] immunologic status,[8] and the presence or absence of the acquired immunodeficiency syndrome (AIDS),[8] circumcision (in men),[9-11] and sexually transmitted diseases.[6,12,13] Other potential factors include plasma HIV-1 RNA levels,[14-17] the presence or absence of chemokine receptors,[18,19] and the use or nonuse of antiretroviral therapy.[20] Improved understanding of the

Discussion questions for Quinn et al.

1. What is the responsibility of journals?
2. What steps should researchers in this study have taken to protect patients?
3. Was consent "informed" in this case?
4. Is it ethical to offer money or free medical care to subjects?

5. What standards should be applied in evaluation: "local", "home", or strictest?
6. Could this kind of study be performed in the U.S. or Switzerland?
7. Should research conducted in developing countries be held to different standards that those applied in the developed countries?
8. Should the approval by government policy (of Uganda), ethics review boards of host and sponsoring countries be sufficient guidelines?

9. How will the results obtained by the study be used in Uganda?
10. Who would most benefit from the study results?
11. Should the manuscript have been published? Is the journal responsible?
12. If this were not HIV/AIDS, but simply syphilis (treatable by antibiotics), would it have made a difference? Should the price of the treatment make a difference?

The Basic Principles of Human Research

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2. **Beneficence –** (1) do no harm and (2) maximize possible benefits and minimize possible harms

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Ethical dilemmas in Quinn et al.
Autonomy

PROS

Providing a level of care above that available in the host country risks coercion. (therefore, justifies not using anti-retrovirals)

CONS

Informed consent assumes the society understands the idea of autonomy, based on a Western understanding of individualism

Having western scientists coming into villages, can create a hierarchy

Ethical dilemmas in Quinn et al. **Beneficence**

PROS

HIV-1 RNA levels were not influenced by anti-retroviral treatment. These cohorts are difficult to obtain in other countries with anti-retroviral studies (maximize benefits)

The subjects see medical personnel regularly, and half of the subjects are treated for their STDs (minimize harm)

CONS

Up to 30 months people with HIV were observed but not treated

It was left up to the sero+ partner to inform the sero- partner

Half of the subjects were not treated for STDs (were referred to free government clinics)

Ethical dilemmas in Quinn et al.
Justice

PROS

Anti-retrovirals are not available as standard of care in Uganda, so they are no worse off than their peers

CONS

The results of the study (heterosexual transmission correlated with viral load) do not benefit the Ugandan subjects as they do not have access to the anti-retrovirals, also because of the clade C subtype dominant in Sub-saharan Africa.

Ethical standards should not depend on the political and economic conditions of the location

Recent studies

- Golden Rice Study (2012): Parents in China were not informed that their children were fed genetically modified Golden Rice (modified to contain beta carotene)
- Experimental Ebola drugs in the Democratic Republic of the Congo (2018): “flexible clinical trial framework” for a warzone, using drugs that are easily to administer