

Challenge study ethics

Zane (<https://wzbillings.com>)

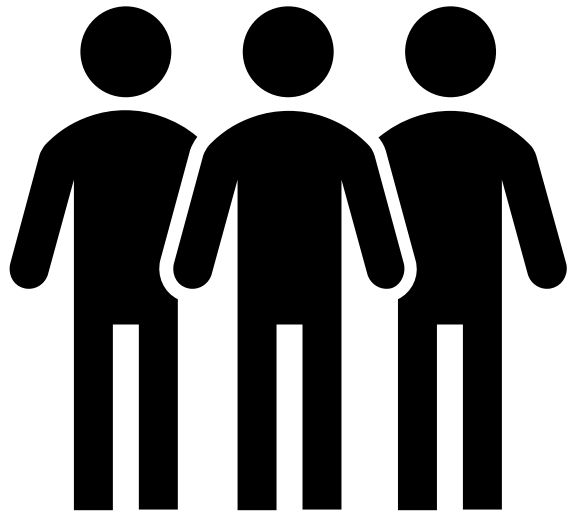
Savannah (<https://smhammerton.com>)

IDIG 2022-10-18

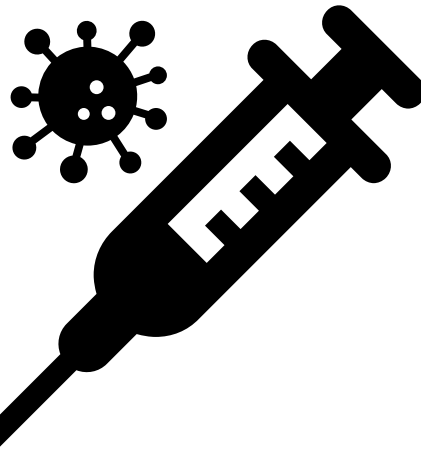
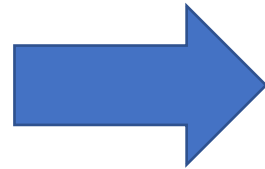
The backstory for this talk

Content warning: Nazi medical experiments, unethical experiments in general

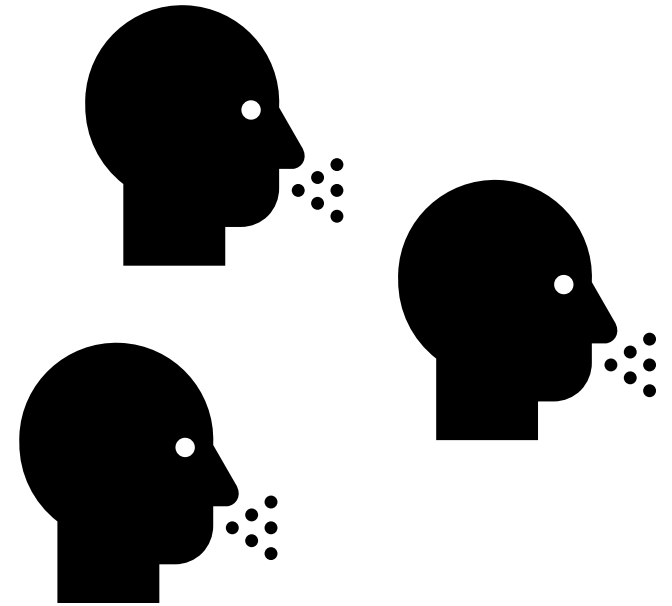
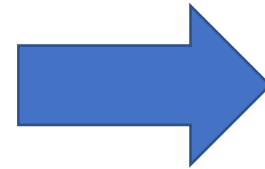
Challenge studies



Cohort of young, healthy people
(usually paid)

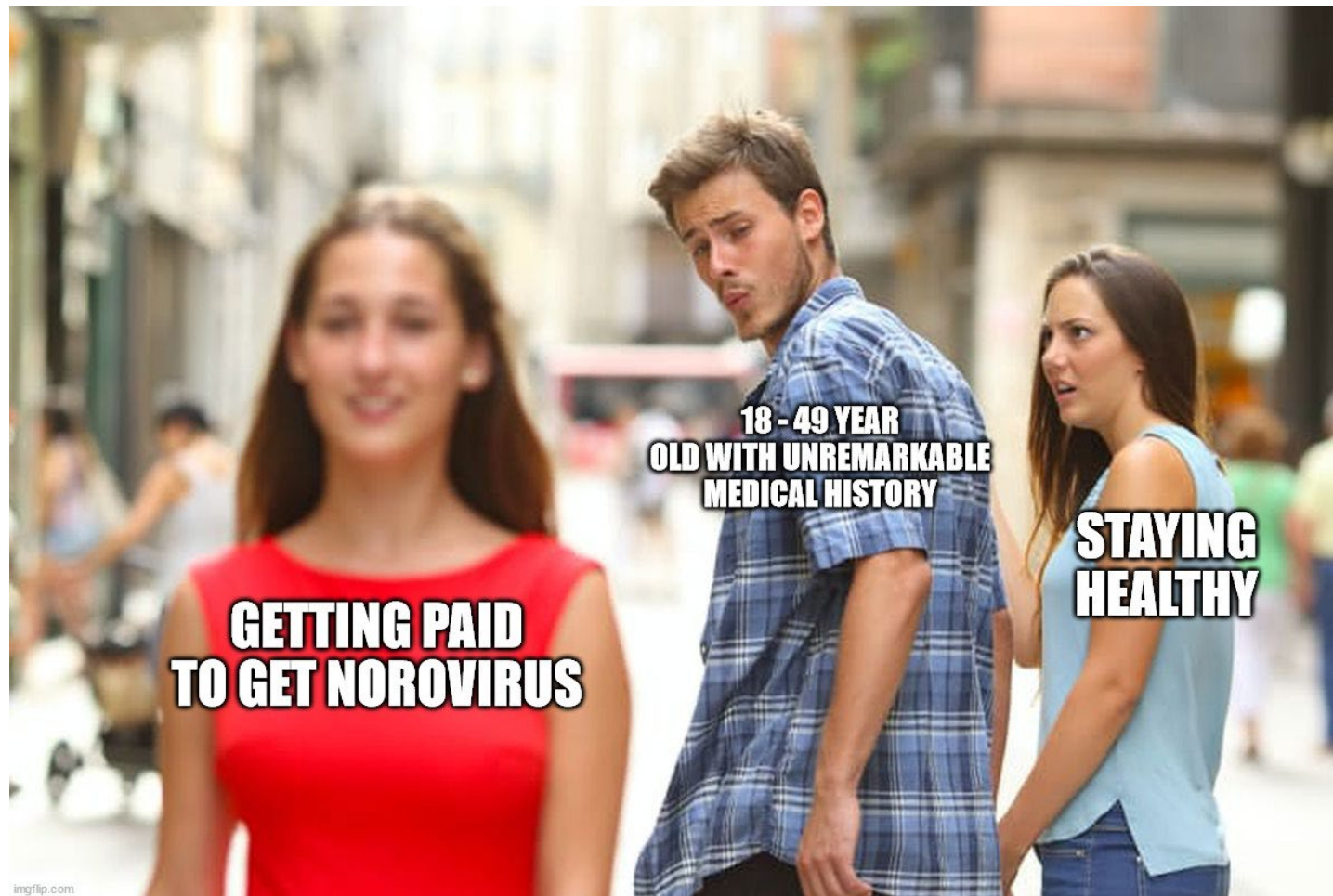
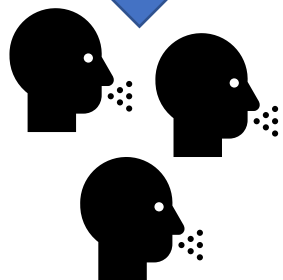
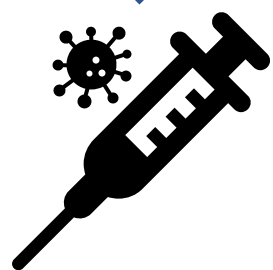
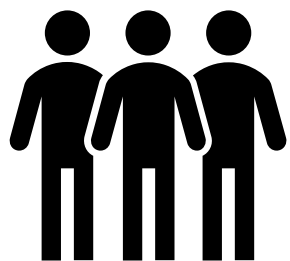


Experimental infection with
“biologic”



Tracking disease progress
and infection outcomes

Challenge studies



Why would we do that?

- Develop vaccines/drugs (e.g., smallpox vaccine)
- Test interventions that lower infection risk
- Understand infection/immune/disease dynamics
- Previously shown to help with:
 - Norovirus (no review 😊)
 - Influenza ([10.1016/j.ijid.2016.05.013](https://doi.org/10.1016/j.ijid.2016.05.013))
 - RSV ([10.1016/j.vaccine.2016.08.086](https://doi.org/10.1016/j.vaccine.2016.08.086))
 - A comprehensive review listed 17 pathogens with established models (<https://pubmed.ncbi.nlm.nih.gov/35862754/>)

Is it okay to do this?

- Usually there is little direct benefit to a participant.
- Potential harms must be evaluated very carefully – challenge studies are usually only conducted on otherwise healthy people. (What makes someone “healthy enough” for this?)
- How to select patients in a just and equitable way? ([10.1111/bioe.12778](https://sites.lib.jmu.edu/elsi-biotech/genomics-justice/historical-context-and-economic-issues/)) E.g., equitability of malaria challenge studies.

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

THE THREE BASIC ETHICAL PRINCIPLES



Respect for Persons

1. RESPECT FOR PERSONS

- INDIVIDUALS SHOULD BE TREATED AS AUTONOMOUS AGENTS
- PERSONS WITH DIMINISHED AUTONOMY ARE ENTITLED TO PROTECTION



Do No Harm

2. BENEFICIENCE

- DO NOT HARM
- MAXIMIZE BENEFITS, MINIMIZE RISK



3. JUSTICE

- EQUAL DISTRIBUTION OF BURDENS AND BENEFITS
- TO EACH PERSON EQUAL SHARE
- TO EACH PERSON ACCORDING TO INDIVIDUAL NEED, EFFORT, SOCIETAL CONTRIBUTION, AND/OR MERIT

WHO Guidance

- <https://apps.who.int/iris/handle/10665/351018>
- Controlled Human Infection Studies (CHIS) = Challenge Studies
- In general, guidance is similar to basic ethical considerations we see in all human subjects research, with some extra relevant points
- Contains a checklist for ethics committees
- Respect for persons, beneficence, justice
- Research/design choice must be justified

WHO Guidance

- Diagnosis and treatment should occur as soon as possible, if not, clear and supportable justification is needed
- Infection control – how will spread to third parties be prevented?
- Withdrawal – after infection, monitoring may be needed even in withdrawals
- Site/participant selection – particularly, high vs low/middle income countries and adult vs pediatric patients
- Informed consent – extra care to ensuring participants are aware of risks
- Compensation – often paid; find balance of proper compensation while avoiding coercion

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Human Challenge Studies in Endemic Settings

Ethical and Regulatory Issues

Additional Resource

- Similar concepts as WHO guidance with more discussion on existing issues/questions and more specific examples
- <https://doi.org/10.1007/978-3-030-41480-1>

What to do about unethical studies?

- Most people agree that using TB challenge data collected by Nazis is unethical (and morally wrong).
- Sidenote: the way we talk about human experiences as “data” can be dehumanizing and unethical in cases like this.
- In less blatantly evil cases, there is more controversy, e.g. Gordon et al paper ([10.1172/JCI103264](https://doi.org/10.1172/JCI103264)).
 - Can prisoners really volunteer for this study without coercion?
 - What was the public benefit of the study?
 - Would any results be equitably distributed to trial participants?

What to do about unethical studies?

- Baruch Cohen's publication on when using these data is ethical (PMID: 11650895, hard to find online but there is a PDF copy in our Zotero group).
 - Are these studies scientifically valid in the first place? If they are, **does it matter anyways?**
 - What amount of societal good stands to come from using these data?
- AMA statement: <https://www.ama-assn.org/delivering-care/ethics/release-data-unethical-experiments>
 - There must be no way to gather the same data ethically.
 - Using the data must result in saving lives.

Should we include papers like Gordon et al (1956) in our norovirus review? If so, should we use data from them?

What pathogens are ok?

- Flu example: pandemic flu strains are often *more deadly* for “otherwise healthy” people (1918, 2009 strains).
- COVID challenge: see, e.g. ([10.1038/s41591-022-01780-9](https://doi.org/10.1038/s41591-022-01780-9)) – challenged before we even understood the long-term effects.
- Hepatitis C (<https://www.1daysooner.org/hepatitis-c>)? Often becomes chronic and treatment is expensive.
- HIV (<https://doi.org/10.1111/japp.12617>) - can risk be minimized enough to justify this?

COVID-19 Challenge Study Ethics

- Commentary submitted April 2020 argued for use of COVID-19 challenge studies (<https://doi.org/10.1016/j.vaccine.2020.06.007>)
- Stated one was already underway in UK, using "related coronaviruses that cause milder disease"
- Should there have been challenge studies this early in the pandemic, before we knew full impacts of COVID-19 on individuals?
- Is a challenge study using a different virus justified if we're not sure the results will really be applicable to COVID-19?

COVID-19 Challenge Study Ethics

- WHO working group developed 8 criteria that should be satisfied for "ethically acceptable" COVID-19 challenge studies (<https://doi.org/10.1016%2Fj.vaccine.2020.10.075>)
- Nothing sticks out as COVID-19 specific – seem to be basic challenge study considerations

Scientific and ethical assessments	Consultation and coordination	Selection criteria	Review and consent
Scientific justification	Consultation and engagement	Site selection	Expert review
Assessment of risks and potential benefits	Coordination	Participant selection	Informed consent

The end slide

- Zotero group link with all references:
https://www.zotero.org/groups/4821110/challenge_study_ethics/library
- Find an online version of these slides here:
<https://wzbillings.com/presentations/IDIG-Challenge-Studies/>