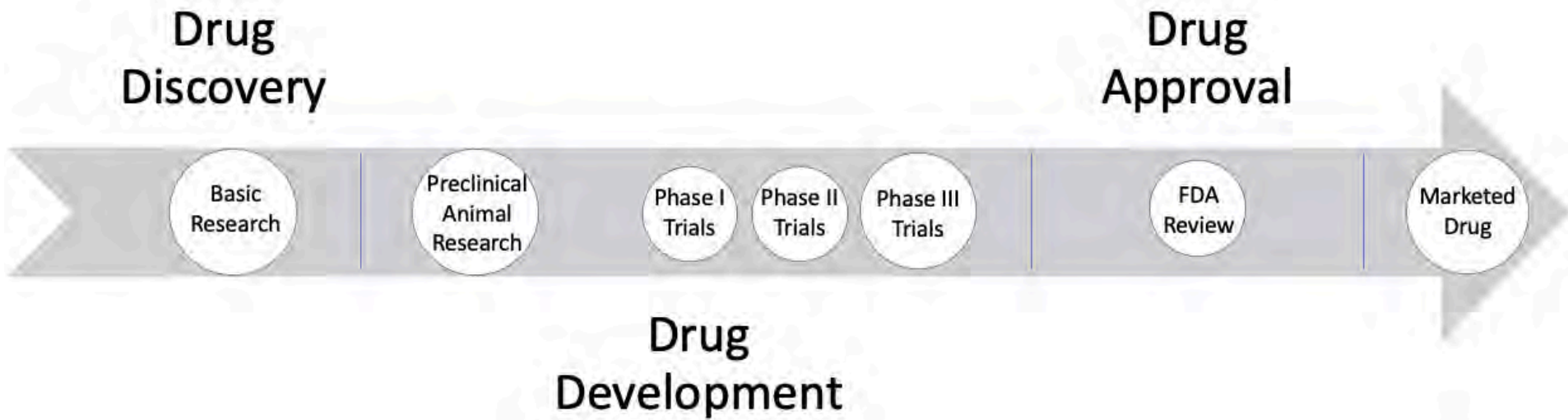


HEALTHY PARTICIPANTS IN CLINICAL TRIALS: ETHICAL ISSUES RELATED TO RESEARCH PAYMENT

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DRUG DEVELOPMENT 101



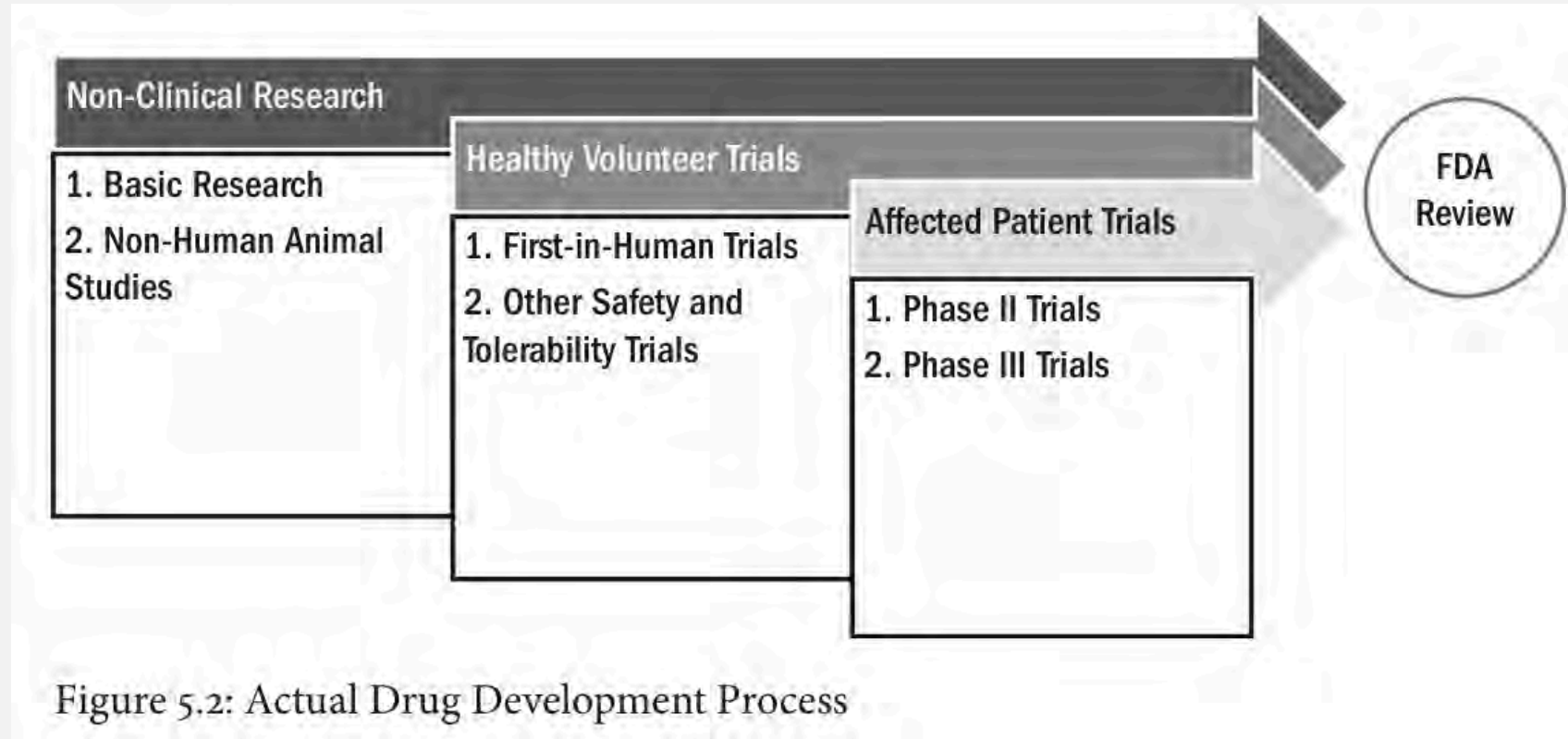
Source: Fisher JA. *Adverse Events: Race, Inequality, and the Testing of New Pharmaceuticals*. New York University Press; 2020.

DRUG DEVELOPMENT 101

Study phase	Primary purpose	Duration	Number of human subjects
Phase I	Safety	Up to 1 year	20–80 healthy subjects
Phase II	Safety, efficacy	Up to 2 years	100–300 diseased subjects
Phase III	Efficacy	2–4 years	1,000–3,000 diseased subjects
FDA approval		25–30% of all products	
Phase IV	Cost benefits	2–10 years	Several thousand diseased subjects

Source: FDA

DRUG DEVELOPMENT



Source: Fisher JA. *Adverse Events: Race, Inequality, and the Testing of New Pharmaceuticals*. New York: New York University Press; 2020.

HEALTHY VOLUNTEER CLINICAL TRIALS

- Phase I safety and dosing studies
 - First-in-Man / First-in-Human
 - Multiples studies to establish “tolerability” of investigation drug (dose escalation)
- Other types of HV studies
 - Metabolism
 - Drug interaction
 - Bioequivalence (*generic market*)

HEALTHY VOLUNTEER CLINICAL TRIALS

- Use of healthy volunteers
 - Rationales
 - Separate the signal from the noise
 - Less risk to participants
 - Availability of participants
 - Ethical rationale
- In-“patient” confinements (days or weeks)
 - Compensation ~ \$200-250/night (\$3070/trial)
 - Preference often given to “repeats”

AEs and Risk

- 65% of all healthy volunteers experience at least one AE
- 1-4% of AEs are serious
- Phase I Catastrophes
 - Deaths at Hopkins (2001) and Lilly (2004)
 - Serious injury at Parexel in London (2006)
 - Death at BioTrial in France (2016)



**HEALTHY
VOLUNTEER
CLINICAL
TRIALS**

PHASE I INDUSTRY

- Most pharma companies have closed their clinical pharmacology units and outsource to AMC's or CROs
- New for-profit facilities up to 300 beds (compared to 12-bed AMC units)



- **Ethnographic Research**

- Observation at 6 Phase I facilities in the U.S. (1 academic; 5 for-profit sites)
 - 2 sites in the Northeast
 - 2 sites in the Midwest
 - 2 sites in the Southwest
- Interviews with research staff (n = 33) and healthy volunteers (n = 235)

*Research supported by the National Cancer Institute (NIH)
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RESEARCH METHODS



PHASE I HEALTHY VOLUNTEERS

- **Demographics**

- Mostly male participants
- Disproportionate number of minority participants
- Most participants between 20 and 45
- Mostly lower income, low educational attainment, and unstable employment history
- Many with a history of incarceration
- Many are immigrants, some of whom are not legally permitted to work in the US

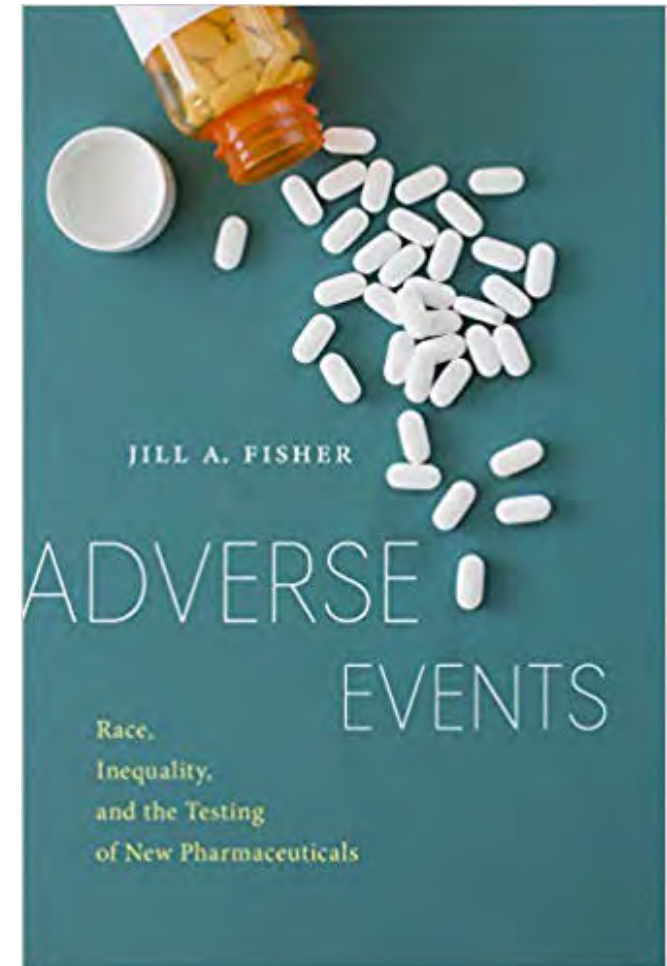


DIVERSITY IN PHASE I HEALTHY VOLUNTEER TRIALS

- Why doesn't the higher percentage of racial and ethnic minorities in Phase I trials feel like a recruitment success?

THE “HIDDEN WORLD” OF PHASE I TRIALS

- **Paradox**
 - Minorities participate in the riskiest studies with no direct medical benefit.
- **My argument:**
 - Racial and economic inequalities in the US create a market of healthy volunteers for Phase I trials.
 - Validity concerns inherent to how the Phase I industry works ensures that new drugs appear safer than they are.



FINANCIAL MOTIVATIONS

- “Louis” (a multiracial man in his late 50s) – re: motivation
 - “I wanted to make some money. . . . It’s definitely not because I want to save the world. . . . Let’s get that on the record right now. No, I don’t want to save the world. No, I need to make money .”

FINANCIAL “DESPERATION”

- “Manny” (a Native American man in his late 20s)
 - “Where else am I gonna get it [income]? Car’s broke down, you know. What are we gonna do? If I don’t pay my parole,* I’m gonna go back to prison. ... That’s pretty much how I see it, is [as] income. That’s for real. And anything else is maybe helping out, you know, seeing what the medicine does too.”

* Some US states make people who are released on parole from prison subsidize the cost of their own supervision (Katzenstein and Nagrecha 2011).

FINANCIAL “DESPERATION”

- “Mirasol” (a Latina woman in her 20s)
 - “What made me decide [to enroll]? Truthfully, hardship. . . . The people that go [to these clinics] very often—, well, there are people who—, how can I explain it? There are people that because of lack of work, we take part in many studies consecutively. And there are people who do not go [to places like this] because they have a stable job. . . . Like years ago when there was steady work like that, we would not even go near [studies]. They would offer [studies] to us, and we would not go near them.” (translated from Spanish)


TEMPORARY STOPGAP

- “Ted” (a White man in his 40s)
 - “I suppose if I don’t find work right away, yeah, I’d be open to it, you know. . . . But I probably won’t do many of these ’cause I’ll get working again and won’t have time.”

PERSISTENT PRECARIETY

- “Wesley” (a Black man in his 30s)
 - “I think I’ll keep doing ’em [studies] until I get old, [until] like I can’t do no more. I mean, I’m gonna always do studies, you know, ’cause I know I can always count on the cash....’Cause sometimes you can get a big chunk of money and you can get out of your debt for a little bit of time, you know. But you’re gonna always be in debt, you know, unless you hit the lottery ... because the bills keep coming back. As fast as you pay ’em, they come back.”


- “Bennett” (a Black man in his late 20s)
 - “Probably the biggest personal gain I’ve ever had is [that] the money comes in a large lump sum.... I’ve made more in a month than most people make in half a year. Longest study I ever did was like 36 days. It was like \$7,300.... Never have I had that much money in my possession at one time.... It’s not a lot of money, but it’s enough to really do something, you know? It’s enough to have somewhat of a free life, you know?... I don’t consider this a career, but at the same time, busting my hump at McDonald’s for \$8 or \$9 an hour and bringing home \$900 to \$1,000 in a month when I can make that in a week, just doesn’t seem feasible to me, you know? Like doing the lab rat thing, I’ve grown accustomed to a certain kind of lifestyle, having lump sums of money whenever I need it, you know, and being able to do whatever I want.”



“DOING
THE LAB
RAT
THING”

- “Bennett”

- “The thing that the lab-rat thing lacks is consistency, you know. If my rent is due and I get into a study and the study gets canceled, my rent [check] gets canceled. If something happens like my muscle enzymes are up or something’s off and I don’t get into the study, I’m screwed. . . . It has its pros and it has its cons, and that’s probably the biggest con for me is just that, you know, it’s not guaranteed. Not only are you competing with yourself, your own body, you’re competing with other people, you know?”



“DOING
THE LAB
RAT
THING”

PHASE I TRIAL COMPENSATION

Study Pay Categories	Total # of Studies (%)	Median Pay Per Day Enrolled (IQR)
\$0 - \$1,999	221 (22.9%)	\$135 (184)
\$2,000 - \$3,999	409 (42.3%)	\$168 (148)
\$4,000 - \$5,999	194 (20.1%)	\$215 (118)
\$6000 - \$7,999	87 (9.0%)	\$233 (95)
\$8,000 - \$9,999	39 (4.0%)	\$246 (75)
\$10,000 - \$11,999	10 (1.0%)	\$293 (114)
\$12,000 - \$13,999	7 (0.7%)	\$263 (100)
Grand Total*	967 (100%)	\$196 (153)

Reference: Fisher JA, McManus L, Kalbaugh JM, & Walker RL. 2021. "Phase I trial compensation: How much do healthy volunteers actually earn from clinical trial enrollment?" *Clinical Trials* 18 (4):477-487.

PHASE I TRIAL COMPENSATION

	Number of Participants		Screenings Per Person Per Year		Participation Per Person Per Year		Pay Per Person Per Year (US\$)	
	Total	n who screened (%)	Median (Min-Max)	IQR	Median (Min-Max)	IQR	Median (Min-Max)	IQR
Baseline–Year 1	131	113 (86.3%)	3 (1-16)	3	2 (0-9)	2	3950 (0-47200)	6720
Year 1–Year 2	131	88 (67.2%)	3 (1-22)	3	1 (0-8)	2	4100 (0-32800)	9059
Year 2–Year 3	130	68 (52.3%)	3 (1-15)	5	1 (0-8)	2	4800 (0-39605)	9824

Reference: Fisher JA, McManus L, Kalbaugh JM, & Walker RL. 2021. “Phase I trial compensation: How much do healthy volunteers actually earn from clinical trial enrollment?” *Clinical Trials* 18 (4):477-487.

CRITICIZING THE INDUSTRY

- “Shirley” (a Black woman in his 30s) – re: exploitation by industry
 - “The drug companies, the academic institutions, or whatever it is, this huge wheel that turns, you know, to power clinical studies, . . . yeah, it’s just so flippin’ capitalistic, you know, when you think about it. . . . Everybody lowering their prices [they pay to participants], the sponsors are just . . . cheering themselves, you know, because they’re actually making more profit off of people [healthy volunteers] who are ignorant and desperate, I would say.”



VOLUNTEERS' PERCEPTIONS OF RISK

- Acknowledgment and Rationalization of Risks
- Risk of Not Qualifying for Studies

ACKNOWLEDGMENT OF RISK

- “For certain people like, you know everybody is different, so I wouldn’t want to take any chances with my health. So this is definitely not something that I wanna make a career out of. It’s something that’s for the time being right now, but this is not something that I want to continue to keep doing.” – “Kasha” (Black woman in her 20s)
- “I treat every drug or every procedure differently. I’m very concerned about every side effect just as I was the first time. Cause this might be the one. You know, like it’s a risk that you’re taking. This is your life and your health at stake.” – “Julius” (Black man in his 30s)


RATIONALIZATION OF RISK

- “Normally they sort of talk about how like we test these [drugs] on rats, but they’ve had at least 10 or 12 times the dose that we’re having. So if like a one pound rat can get through it alright, I’m sure I should be okay, you know... So I just figure I’m safe enough.” – “Alex” (White woman in her 40s)
- “I think the best time to do it is if you're young and your body has a better chance of repairing itself. When you are old, when it's just you know, there's not much left in the tank, you know? So I don't know, I think I'm in the right time of my life where I feel like I can fight off a lot of infections or I could recuperate from a lot of things.” – “Troy” (Black man in his 20s)

RATIONALIZATION OF RISK

- Trust in Research
 - “So, I’m kind of trusting in that they have to adhere to the IRB, whatever it is, you know. So, I kind of have faith in the process they’re doing, and whatever they catch, whenever they catch something. I know that it’s part of protocol to let it be known to everybody, like immediately, you know what I mean? So, if something happens to a prior group... So, I kind of go in with a sense of security that everybody’s doing what they’re supposed to do, you know.” - “Arnel” (Asian man in his 50s)

- *Construction of risk divorced from particular studies*
 - Failing a screening
 - Picking studies carefully
 - Example: Hep C drug study at site in Northeast
- **Study and post-study routines**
 - Positive and negative behaviors



RISK OF
NOT
QUALIFYING
FOR STUDIES

BODY MAINTENANCE

- “When we get out of here, well, basically I’m on like a vitamin regimen. So, basically, we’re putting back everything they took from us. Because it’s vital, for one, to get into the next study. How much blood you gave, and depending on how many studies you do on a yearly basis, you know, your hematocrit, your hemoglobin, all that stuff drops because they’re taking the blood from you. So, you gotta make sure as soon as you get out of here, you’ve gotta say, “Okay, gotta take this blood builder. I’ve gotta drink this smoothie. I’m gonna eat this. I gotta make sure my cholesterol is right.” So it’s like we become like small pharmacists, dieticians, and we tell each other, ‘Oh man, take spirulina.’” – “Eddie” (Black man in his 40s)

BEHAVIOR CHANGE

- “When I first started doin’ studies I was smokin’ weed. And that’s what got me to stop, stop smokin’ weed ten years ago. I did a study in Philly at [name of facility removed] and the guy said, ‘I’m not goin’ bar you this time, but don’t ever do it again’... Ever since then I stopped smokin’ weed... because I got used to not getting high off of weed and then eventually I just said, you know, I can live like this. You know another thing, I stopped drinkin’, too, cause your liver enzymes go up.” – “Don” (Black man in his 40s)



WHAT ABOUT FINANCIAL RISK?

- Bioethics and IRB concerns have largely focused on undue inducement and coercion, but can compensation for research also pose a risk to healthy volunteers?

COMPENSATION AS TAXED INCOME

- Healthy volunteers are “independent contractors” for tax purposes.
- Consent forms provide limited information about tax liability.

{Waltz, Margaret, Arlene M. Davis, & Jill A. Fisher (2023) “‘Death and Taxes’: Why Financial Compensation for Research Participants is an Economic and Legal Risk.” *Journal of Law, Medicine & Ethics* 51 (2): 413-425.}

COMPENSATION AS TAXED INCOME

- Healthy volunteers' awareness of tax liability
 - Initial belief that it is “tax free”
 - Shock of the 1099
 - Navigating the tax system as an entrepreneur
 - **Avoiding reporting trial income**

COMPENSATION AS TAXED INCOME

- Healthy volunteers' awareness of tax liability
 - Avoiding reporting trial income
 - “For every time that you take that money..., it’s technically, right at that moment, tax-free. If you ride [under] the radar, which I did this in the beginning of my study career, doing studies, I did just enough whereas I didn’t have to pay taxes because I was scared to pay money, ‘cause I didn’t know how I was gonna pay it. So, I was like, wow, if they tax me off this tax-free money, so to speak, I may owe them a lot of money... That’s when the similarity of the drug trade and this trade go hand and hand because at that point, you’re doing something semi-illegal... You’re not trying to pay your taxes... The drug dealer, he’s out there trying to avoid the police. He’s trying to stay a step ahead of them. I’m trying to stay a step ahead of the IRS.” – “Roman” (a Black man in his thirties)

COMPENSATION AS TAXED INCOME

- Healthy volunteers' awareness of tax liability
 - Burden of tax debt
 - “I probably will owe about \$35,000 [laughs]. And most of that is because what the IRS sees on all those years is me doing clinical trials where they didn't take any taxes out. You know, I just got paid in checks without any taxes [withheld], so I'm supposed to pay taxes to the IRS all those years for all those clinical trials.” – “Steve” (a white man in his 40s)

COMPENSATION AS TAXED INCOME

- Perverse incentives stemming from tax liability
 - Curbing trial participation to stay below income thresholds
 - Enrolling in new clinical trial to pay last year's taxes
 - “Some people that have put in years [doing studies] and the first thing these pharmaceutical companies might say is, ‘Well, look at the money you’ve made over the years,’ but it’s not tax-free... That’s why we got to do another study, so we can pay taxes [laughs].” – “Lee” (a Black man in his fifties)

COMPENSATION AS TAXED INCOME

- Taking advantage of healthy volunteers?
 - Less compensation that it seems
 - “After, you know, minus the taxes, the time, the travel, the this, the that, you know, how many screenings you have to go to and all, you know, it just, at the end of the day, it just-, you know, it was a lot less than what you actually thought you were making.” – “Travis” (a Black man in his forties)


COMPENSATION AS TAXED INCOME

- Taking advantage of healthy volunteers?
 - Taxed when taking on physical risk
 - “I don't think we should have to pay taxes on this money.... Because you shouldn't have to pay taxes for a thing like this because we're doing nothing but service to the people. And nothing bad comes out of this, it's a hundred percent all good. Only bad that's coming out of it is if something happens to you in a study to you, your own person, and then you have to deal with [that]. Then, you didn't get much from it but that one check, and then you still have to pay taxes on it.” – “Sylvester” (a Black man in his twenties)



CLOSING THOUGHTS

- Regulatory system governing drug development established an industry for healthy volunteer trials.
- Healthy volunteers are those who are incentivized by financial compensation and have the time and ability to be confined for long periods.
- The US context of social and economic inequalities funnels people of color into these trials because they often do not have better options to earn income.



CLOSING THOUGHTS

- Ethical issues also tied to “promise” of financial freedom.
- Compensation may appear substantial but does not provide financial security and even comes with financial and legal risk from taxes.



QUESTIONS, COMMENTS?