ADVERSE EVENTS: RACE, INEQUALITY, & THE TESTING OF NEW PHARMACEUTICALS

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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

PHASE I CLINICAL TRIALS

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

PHASE I 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)

PHASE I CLINICAL TRIALS

PHASE I INDUSTRY

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

https://jalr.org

RESEARCH METHODS

- 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)

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PHASE I HEALTHY VOLUNTEERS

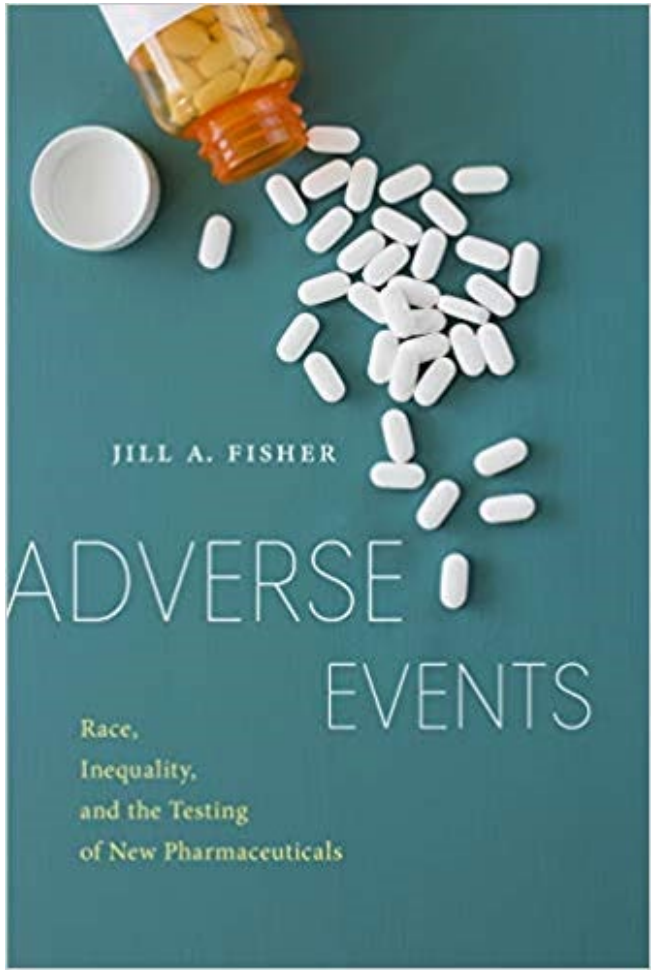
- **Demographics**
  - Mostly male participants
  - Disproportionate number of minority participants
  - Most participants between 20 and 45
  - Mostly lower income, low educational attainment, and unstable employment history
  - Many with a history of incarceration
  - Many are immigrants, some of whom 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).

- "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"

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
- Metaphors of Risk

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)

RATIONALIZATION OF RISK

- Trust in Research
  - "And you have to be healthy. That's the one thing that comforts me. At the end of each study you have a physical and then you go from a physical maybe to a screening. So you get checked out thoroughly; all your blood work, your lab work, your heart rate, EKGs and blood pressure, everything to make sure that you're healthy before the next study. So that means that you're okay. So that's comforting to me to know, there's a sense of having a physical like you're always healthy." – "Julius" (Black man in his 30s)

RISK OF NOT QUALIFYING FOR STUDIES

- *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

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)

SERIAL PARTICIPATION AND TRIAL PROTOCOLS

- Washout periods: Risk-taking activity

  "I was doing it before as a living. I would get out of one study and go to another study. Back to back, back to back, back to back. So, you know."

  Were you ever nervous about doing that?

  "In the beginning I used to be. But then once you get going, it's like nothing. It's like because nothing bad happens to you, and then, yeah, you think everything is all right… I thank God too because I know, I know something could happen because I listen to the news, and I know that if you take too much drugs and stuff like that, it's not good for the body. So I'm aware what chances we take." – "Javier" (Latino man in his 40s)

SERIAL PARTICIPATION AND TRIAL PROTOCOLS

- Washout periods: Just guidelines
  - "I would want to flush everything out of my system, and for the most part I really, really try. But like I said [before], for women, it's really hard to find studies.* So you have to be calling and you're hoping that the date winds up giving you sufficient time to really, really flush out your system. But we know from doing studies that your system is actually flushed out far earlier than the time that they say. So it's not that important. But I try to give it as much time as possible, but if something comes up, I'm gonna take it. I'm gonna take it…And that means I'm not gonna tell the truth on my informed consent, but I'm, I'm pretty positive that it's all gone by the time I go into something else." - "Tia" (Black woman in her 30s)

METAPHORS OF RISK

- "When you have kids…, you have to do what you have to do to maintain. Anybody can sit around and criticize somebody, but the true soldiers get out there and do what they gotta do to take care of their families." – "Marcus" (Black man in his 40s)
- "I would not recommend anybody to do studies unless they had to do it. If your buddy had a financial problem, children, or your mortgage, something serious, but just don't go and do it because you think it's, it's a fun thing… You've gotta be a soldier." – "Kevin" (Black man in his 40s)

METAPHORS OF RISK

- **Soldier trope as expression of altruism or identity?**
  - "Oh man, my mom [she says], 'Oh! It's crazy what you're doing… You gonna end up getting hurt and your organs are gonna fail.' And I'm laughing 'cause anybody [who] doesn't understand something they're gonna say that. You know, they're gonna have fears…. I said … 'Actually, I'm like a medical soldier for you. I'm the guy who goes out in the field and I take the first hit. I make sure that you can live your life… with these medications. They test 'em on us first, then they test 'em on phase 2 or phase 3, make sure they're safe for people that are sick, and then, they come to you.' I said, 'So, I'm doing a great thing for you. Cause without me, it'd be you, you'll be the experiment.'" – "Eddie" (Black man in his 40s)

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

- System of clinical research rewards high risk behavior among serial participants
  - Unmonitored washout periods
  - Inclusion-exclusion criteria may induce women to take on riskier studies
  - Male volunteers mobilize a masculine trope that creates a parallel with another risky profession in order to make sense of their experiences
  - Health as a commodity that needs to be produced, which might have its own benefits outside of clinical trials

PRACTICAL IMPLICATIONS

- Social inequalities outside of realm/control of biomedical researchers and oversight bodies, ***but***
- Lessons for IRBs (Walker et al. 2022*)
  - Ethical Criteria for Phase I HV Trials
    - Translational science value
    - Fair opportunity and burden sharing
    - Fair compensation for service
    - Experiential welfare
    - Enhanced voice and recourse

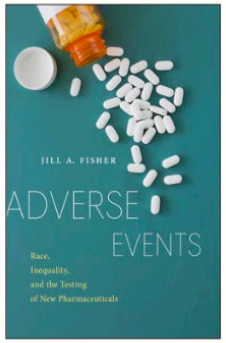
Walker RL, MacKay D, Waltz M, Lyerly AL, & Fisher JA (2022) "Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials." Ethics & Human Research 44 (5): 2-21.

PRACTICAL IMPLICATIONS

- Lessons for IRBs
  - Fair opportunity and burden sharing
    - Require broad-based recruitment methods.
  - Fair compensation for service
    - Ensure that study compensation is commensurate with protocol requirements and disbursed in a timely manner.

Walker RL, MacKay D, Waltz M, Lyerly AL, & Fisher JA (2022) "Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials." Ethics & Human Research 44 (5): 2-21.

QUESTIONS, COMMENTS?



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