

Recall This Book 30: In Focus

Nir Eyal with JP “Challenge Testing” for a Covid Vaccine

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John Plotz:

From Brandeis University, welcome to Recall This Book where we assemble scholars and writers from different disciplines to make sense of contemporary issues, problems and events. I am John Plotz and we have actually a most unusual kind of guest today because we are being unusually contemporary. So I'm very pleased to welcome Nir Eyal who is the Henry Rutgers Professor of ethics and the director of the center for population level bioethics at Rutgers University. Nir is also the lead author of a striking recent article in what is actually, I have to say one of my father's favorite journals, the *Journal of Infectious Diseases*. So the article coauthored with Harvard's Mark Lipsitch and Peter Smith is called “Human challenge studies to accelerate coronavirus vaccine licensure.” And if that's not revelatory enough I should say there's a recent interview with him, which I highly recommend in the prestigious journal *Nature* with this explanatory title, “Should scientists infect healthy people with the Coronavirus to test vaccines.” So, Nir welcome. I know that you're only doing this because my beloved friend Leah Price made you do it. But I really appreciate your coming on nonetheless.

Nir Eyal:

No, it's because you're my beloved friend as well.

John Plotz:

I appreciate it. So Nir, can I just start the ball rolling by asking you to tell us about this article since it only came out on I think March 30th. I doubt our listeners know much about it yet. So set it up for us.

Nir Eyal:

Sure. So it is very important to accelerate finding a vaccine that works for coronavirus as soon as we can. With projections of up to 20 million people

dead this year alone. If we accelerated by a month or two months and we get earlier out of the bind we are currently at between killing our old people and, and devastating the economy, then we save maybe many millions of lives. We came up with the proposal for how to accelerate that process. The most time-consuming part of testing vaccines is the so-called *efficacy testing*. After you're done with the initial safety testing and checking that there was any response in the immune system, you moved to checking if the vaccine actually works. If it stops people who are exposed to the virus from getting infected. And the way that's usually done is you'll give thousands and thousands of people, either the vaccine that you're trying to check or some control, perhaps placebo, perhaps another vaccine. And you'll see if month later after, presumably even though everybody's trying to isolate themselves, et cetera, there was more infection in the arm that did not get the vaccine that you're checking. That's a good sign that this vaccine works, that it's efficacious, that it stops the infection from occurring.

John Plotz:

Okay, so Nir just to stop you there. So the classic trial breaks down into a safety phase, which is indispensable, but you're saying is relatively short, in which you establish that the vaccine is, you know, not going to cause people to drop dead immediately or cause some other bad side effect. And then once you're past that, which you're saying can be relatively quick, you enter into what is potentially a much longer period in which you give a bunch of people the vaccine and then you just send them out blind. The world becomes your laboratory at that point. So let's say you have a thousand people, 500 of them get the vaccine, 500 don't. And you just see of those 500 did a lower number in the wild, get coronavirus then the 500 other people who've got a placebo instead.

Nir Eyal:

Yeah. It may actually be closer to maybe 5,000 or five dozen, yes. Okay. That could take months because everybody is doing what you and I are now doing which is hiding in their homes and trying not to get any exposure. So you really need for, a lot of them so that it's meaningful and you can actually base credible science on it, to make the mistake and get exposed at some point. And

then you can, with assurance say this works. We propose a much shorter alternative to that phase to that time-consuming phase of efficacy testing.

John Plotz:

Totally clear. So far. So now you have a, you have a way to replace that “in the wild” period with something else.

Nir Eyal:

So instead of in the wild, you could exposed people artificially to coronavirus. You will get results very soon thereafter. You don't need this big, big, big group of people. It could be maybe a hundred people. You don't need these many months of waiting and the doubt about whether it will even ever reach a conclusion that you have with the standard efficacy testing. But what you have done is you exposed people deliberately to coronavirus, which is a virus that is currently killing so many people and for which we don't have a cure. So doing that initially raises a big ethical question. Thankfully, I think that there are excellent answers as to why this is perfectly ethical.

John Plotz:

Okay, so let to near, let me stop you right there. So that sounds totally clear. So, just to be clear, has this idea of exposing people to the very disease that you're trying to protect them from ever been proposed before with earlier diseases?

Nir Eyal:

Yes. we do challenge trial. So challenge trials means you challenge them by exposing them to the pathogen that you're checking. This is how we come up with the seasonal flu vaccine. We do that to try to develop countermeasures for typhoid, for malaria, for other diseases. Historically some of the greatest advances and greatest ethical abuses in the history of medicine happened when people were sometimes exposed to very deadly vaccines. We believe in this case you could do it in a way that is ethically, initially very concerning. But eventually once you think about it enough actually something that is ethically fairly unobjectionable.

John Plotz:

Okay. So you've mentioned objectionable stories of the past and I'm sure we'll get to them, but you also mentioned seasonal flu. The reason that the challenge trials of seasonal flu are okay is that fatality rates are so low that it doesn't really raise any eyebrows. Is that, is that the reason or...?

Nir Eyal:

Yes. Usually when people justify doing that, basically taking a healthy person who doesn't need any vaccine or treatment or and or certainly not viruses and exposing them to a virus to check if some vaccine works is not very risky in its own right. It's not a very deadly virus. It's not commonly deadly and things of that sort. We are trying to rely on a different justification in this case because this is a deadly virus.

John Plotz:

So Nir I'm with you on your explanation of how it differs from something like a seasonal flu challenge. So say more about the logic that you think underpins using it for this potentially deadly disease.

Nir Eyal:

A major difference is that in this case there aren't just risks which can be minimized. There are also benefits to the participants and specifically benefits of the very same category as the risks. And it's possible that because of the very special circumstances of the current pandemic, people will avoid the risk of the worst scenarios of coronavirus disease if they participate in the trial *more* than they would outside any trial and more than they would under a standard efficacy trial. It's also very likely that we would have fewer adverse events (you know, bad medical outcomes) under this trial, which has only maybe a hundred participants than under a standard efficacy trial, which has maybe 10,000.

John Plotz:

I see. So you're saying not only, you're saying there's a cost in lives in terms of the longer duration of those studies, but you're also saying that because those other studies involve more people than this study would –[that] even within the study itself the costs would be lower for this kind of challenge.

Nir Eyal:

Yes. And the most central point is maybe the first point, which is that per participant it maybe a good gamble, if you will, to participate in the trial. They are improving their prospects of not dying from coronavirus if they participate in the trial compared to either not participating in anything and compared to participating in a standard efficacy trial, which is the main competition here.

John Plotz:

How, how so?

Nir Eyal:

It has to do with something that was not true for the other diseases for which challenge trials were usually done. It is, it has to do with the fact that so many of us would get exposure and potentially infection anyhow. This is a pandemic that according to some models, it's likely to infect eventually maybe 50% of the world's population. The world is a big place there would be different areas the outliers would have maybe significantly above that. So if the trial lists select very carefully which area to hone in on and go for areas where people at that point and in future point are expected to have a lot of infections, then first the difference between the near certainty of getting infected outside the trial and the complete certainty inside the trial is not so dramatic. Yes. But also if they stay outside the trial, they are likely if in the worst-case scenarios if things go really badly, they're likely not to have the care that they need.

We're going to recommend to trialists to recruit only young and healthy people whose risk of the bad scenarios is anyhow low. But if they want this assurance I'm, I'm in the worst case and are going to have a place in intensive care unit. I'm talking to you now from outside of New York City and New Jersey. I'm not sure that I could get a place in the intensive care unit if I needed one right now. That for them might be quite rationally a more

significant benefit then changing primarily the timing at which they get infected much more than the probability that they get infected.

John Plotz:

So Nir, this is really interesting. I'd like to, can we just sort of dig down on this as a philosophical question? I want to make sure I understand what saying. So you're saying, I think it goes without saying here, but maybe I'd like to hear you say it, that you are assuming volunteers who are willing to take part in such a trial, like you're not going to, there's not going to be any coopted populations. People are going to positively opt in to do it.

Nir Eyal:

So I mean that's maybe worth just underwriting. So one of the huge differences between some of the historical abuses and how we nowadays do challenge trials, not just in this case, but also seasonal flu, in malaria, et cetera. And especially in this case I would say, because this is, you know, a big deal, the quality of the informed consent would have to be very high. We do not want children or prisoners or recruits or the researcher's own students and et cetera, et cetera, et cetera. We, it's got to be very, very voluntary and very informed. So you're absolutely right. And that is part of the justification. So the fuller story is something like, given that it's a balance of benefits and risks that I think, and we can dig more into this is, is one that is not clearly awful for the individual, who are we to stop the individual from making a choice that is legit helpful and comes with their own full comprehension of volunteering?

John Plotz:

Yeah. So, so this is what I wanted to say more about. So thanks for clarifying that. So the question is, so it's not enough that people are willing to sign up for it. You also, you feel that you have to make, if you will, a kind of two-ply argument. One ply is they are consenting to do it. They're choosing to do it, whether it's through altruism or self-interest or whatever, they are making that choice. But the second level is you, you have to believe that the choice itself ... can be kind of legitimated rationally, like apart from their own subjective decision to do it.

Nir Eyal:

Totally right. I mean, I'll say, Oh, I'll say what you said concisely in a slightly longer way. There are two separate requirements in the list of--there are some canonical lists of what you expect in a research study, one of them has to do with informed consent, and another one has to do with the balance of risks and benefits for the individual, if society's gaining enough from this study to justify any negative balance for the individual. This case, I think that this balance looks pretty good. It's not like those cases where you're starting to say, "Oh my God, there would be huge social benefits and for some reason this person is willing to sacrifice themselves. But it would be utter sacrifice. There is, you know, the certainty that we would kill this person or maim this person for no good reason for their health. "

In this case actually turns out it might be overall beneficial to the person certainly could not be highly, highly prospectively bad for the person.

John Plotz:

Can I just within that context, Nir can I ask a hypothetical, and I really don't know the facts here, so you can correct me on the facts, but what about the argument that said the people for whom it would be beneficial here would tend to be people who for other reasons would lack decent health care? You just mentioned you couldn't get to the ICU, but let's just say hypothetically, there's you, Nir, with a really good health care program, which means you probably could get an ICU bed. And then there's another Nir 2, a Near-Nir, who doesn't have a good healthcare plan, he's only on Medicaid. And he feels that without doing this trial, he doesn't know whether he would get ICU. So do you see what I'm asking? Could there be like a utilitarian bias there, which would select for people who felt that, man, if I don't get into this study, then I'm going to be, you know, left out in the cold.

Nir Eyal:

Yeah. You know, I think you're right that there is this possibility. I think that the world is a big place and if trialists have the budget and I think they must have this must be given the budget in this case because our economy really depends on getting this done. If the trialists have the budget to jet around the world, the only, you know, just the hundred people they need then very secure

from infection and everything else, flights around this trial. They could really select people who are the best candidates from an ethical standpoint. Perhaps indeed homing in on people whose plights comes from injustices would be exploitative. If the plight are very, very severe, maybe in some sense they wouldn't have any choice except to participate in the trial and although that's a little harder to press if you're talking about young healthy people who are not infected. So it's not quite the same thing as sending somebody who already has a disease. And their last hope is to participate in the trial that you will only get them into some trial, which is bad for them or whatever. So, but the, the point is you don't need to home in on these people whose plight comes from injustices such as uninsurance, underinsurance in this country. Who knows in a couple months maybe Stockholm will be the world epicenter of infections. People there are insured. You could select if you want for high socio-economic status people for maybe in terms of comprehension, maybe it's better to enroll only university students. And I'm optimistic that we would have that crowd.

Since we published the article, we have been inundated with emails from people who want to participate in those trials. They don't understand that we are not trialists. We're just dudes wrote an article and we've been some friends who have been collecting those. The friends' names are Josh Morrison and Kate Wharton. They have over 800 names down. And I've anecdotally kind of, I sometimes looked at the, you know, details that people write us before I forwarded the names and they are, you know, often students from the best universities in North America and Europe. But there are, it's a famous disease. A lot of people might volunteer without having the strife that you're describing and the trialist might be instructed to select against people whose plight comes from that.

John Plotz:

Yeah, it's interesting. I mean, I was just playing through the ironies in my head where you might have a situation that the result is that people get excluded from the trial precisely because they are in socioeconomically comprised uh compromised situations. But I take your point...

Nir Eyal:

It is an interesting question. There is a question as to, you know, the, sometimes people say, you know, the one worst thing than being exploited is not being exploited. Right. So how are we helping the workers in you know Bangladesh?

John Plotz:

By not buying the tee shirt.

Nir Eyal:

Yeah, exactly. And then, yeah, they don't have a job. It goes to China. So the ethics around exploitation is a complex thing. I didn't want to commit one way or the other in this article, but certainly trialists if they are with you, if they don't want to exploit that to higher priority than giving an opportunity to everybody to be part of the trial. Sure. They could go that way. They could just select accordingly.

John Plotz:

Have you thought about whether there's a Kantian versus utilitarian conflict here or,

Nir Eyal:

My hope is that in this case there is a broad umbrella of ethical approaches that would endorse such a trial. Utilitarians would say this would save millions of lives. Maybe they would go ahead even without high quality consents, maybe they would go ahead even if it was awful for the individual. But they would go ahead.

Or maybe let me discuss two kinds of anti-utilitarians. Most anti-utilitarians and anti-consequentialists (people who are not judging what to do based on the goodness or badness of the consequences) Most of them are so-called threshold deontologists. They say, in principle, there are certain types of acts that you should not perform: you shouldn't be torturing innocent. You shouldn't be lying. You shouldn't be breaking your promises. But if the consequences were absolutely dramatic, sure. Then the threshold can be overridden by these incredibly important consequences.

John Plotz:

And the word, the phrase you use there was threshold deontologists. So a deontologist is somebody who defines their ethics in terms of duties that are absolute or understood as like the guiding principles for life.

Nir Eyal:

There are different definitions for deontology, but for our purposes right now, maybe the most useful one would be, to identify it as just the very same thing as anti-consequentialist. Anybody who says it's not just the consequences. So I'm a threshold deontologist if I say it's not just the consequences when the consequences are, when the stakes are small, you should go with not lying. You should go with not breaking your promise. Right? Shouldn't break a promise just to achieve a minor benefit. Okay. If I can prevent a Third World War, if I can save a million lives by breaking a promise, I should probably break the promise.

People like that would say here, I think because we are talking about very large numbers of lives. Yes, maybe even they could--and that's the most common view among nonconsequentialists--Even they could agree we should go ahead with the most rapid way of examining our vaccines. No matter what to in this case because so much is at stake.

John Plotz:

And and the argument there would be the deontology would be you should never knowingly infect somebody with what could well be a deadly disease, but the threshold would be you can knowingly infect them if they give their consent and the consequences could be the saving of thousands or millions of lives.

Nir Eyal:

Yeah. I would put a different way. I would say that the deontological part is something like you should not sacrifice individuals by risking them greatly and not giving them any benefit and not waiting for them to consent and not all the things that we do, which are fair and right towards study subjects. You

could just do it because it serves some collective purpose. They would say if the collective purposes urgent enough, then all things considered despite hating to do it, you should do it. There are the most extreme nonconsequentialist who are absolutist. There are very few of these in the history of 20th century, 21st century ethical thought. They would say you should do the right thing by individuals, period. It's not, this is, this cannot be overwritten by some collective benefit.

And for these people I would say even they could agree to what we're proposing because we are not doing the wrong thing by individuals. We're doing the right thing by individuals. When you donate money or if you'd donate a kidney or people don't say, *Whoa, Whoa, donating the kidney is not in your medical interest. You can't do to it.* If you tried to donate your heart, okay. People might say, *I'm not sure I'm going to help you do that one.* But my point is really that this one is after you think about everything is much more like donating a kidney...actually an intervention them, it's beneficial for you. So absolutely no ethical problem. It's a no brainer.

John Plotz:

Yeah. The donor kidney is a great example actually because I totally get that right. I mean I have a friend who donated, who donated I think actually half a kidney as it turned out to her, to her a close relative. And yeah, no, that's a great example because it puts you at a slightly heightened risk going forward, but you choose to do it anyway because it's, you think it's the right thing to do for someone you care about. In this case, the someone would be like the human race in general.

So have you heard any counter-arguments that give you pause?

Nir Eyal:

I've heard the argument that you come up with John and that gave me pause about the potential for selection of people whose bad background circumstances come from injustices and the worry that this is exploiting or this is making them have no other choice.

There are also some practical points. Some people point out that in challenge studies, there are some additional stages: you need to take some time to develop the virus in the lab. You need to do then do some preliminary studies to identify what is the correct dose of the virus to give to the volunteers and

you need to create these centers. We didn't mention that it's very important that all of this must be done in a very strict isolation centers where the volunteers couldn't infect others. In fact, that could be part of the attraction. Somebody might think, *I have aging parents, they're immunocompromised*. I'm quoting actually from some of the emails that people sent me. *I want in a very controlled environment to get rid of this infection. I'm likely to get infected anyhow. I want get rid of it with doctors around me to jump in if I need help*. You're not out there in the field. And in an environment where I absolutely cannot, infect my parents, right. Then I come back home and I know that I can go back to my maybe essential job that I cannot avoid. Yes. And I could not, you know, ever kind of infect them. So we are right.

John Plotz:

So that actually like that turns the concept of what would people have been talking and begun to talk about the immunity passport. That becomes more than just kind of an iPhone app. It's actually a way of being in the world. Like once you have that immunity passport, you actually have a level of safe action with other people. Cause I think about that with my aging parents all the time as well. You know, that question of like who should be around them?

Nir Eyal:

Well you can't join the trial, John, you're too old.

John Plotz:

I noticed that you said, well that's only because you set it at 45 you know, if you set it at 53 then I'm golden. You know, we always think about what, when special circumstances arise. Like we just heard this debate about the Wisconsin primary as to whether that was an ordinary or an exceptional circumstance in terms of the constitutionality of postponing that election. And we heard the Supreme Court say, Oh no, it's, there's nothing extraordinary about it, which seems like an extraordinary decision in light of the pandemic. But, but the question I want to ask you is basically about the status of the *exceptional circumstance* because I think I could interpret what you're saying in one of two ways.

And the first way is you might be saying that pandemics cause exceptional circumstances in which we would actually have to put ordinary ethical laws in

abeyance in order to respond to this state of exception. And the second would be that you're saying that under the, the rules of pandemic, let's call it like the rules of war, the changed circumstance allows you to kind of revisit your ethical principles and see if the ethical principles result in different actions now, given the way the facts have changed. So are you making an argument for the former, for the sort of state of exception around ethics or for the latter: that our same ethics now call for different outcomes based on different circumstances.

Nir Eyal:

My take on this is that we can reach to the same old principles of research ethics and find ample justification there. This could be done with perfectly informed consent. It could be done without a very problematic risk-benefit ratio. It looks initially like it's an absolute aberration, but once you think about the full picture, it's not.

John Plotz:

Great that, that, that's what I thought you were saying. Thanks. That's very, that's very clear. Well Nir you. You've sold me, so I'm going to go fix my passport right now. So it looks like I'm 44, then I can sign up. I'm going to buy a wig also. It's going to look a lot like your hair, right? Yeah.

So I will just say quickly that Recall This Book is hosted by John Plotz and usually Elizabeth Ferry with music by Eric Chasalow and Barbara Cassidy. Sound editing by Claire Ogden, website design and social media by Kaliska Ross.

We always want to hear from you with your comments, criticisms, or suggestions for future episodes. You can email us directly or contact us via social media and our website. And if you enjoyed today's show, please be sure to write a review or rate us on iTunes, Stitcher, or wherever you get your podcasts. You will of course find links to Nir's article, the interview with him in *Nature* and various other related material on the episode webpage at recallthisbook.org. So check out other recent conversations including with writers such as Zadie Smith, Cixin Liu and Samuel Delaney. So Nir, thank you so much.

Nir Eyal:

Thank you, I really appreciate it.

John Plotz:

And at an incredibly busy time for you, I'm sure. So thanks a lot and thank you all for listening.