



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT
Human Subjects Protection Reform

Ezekiel J. Emanuel, M.D., Ph.D.
Former Chief, Clinical Center Department of Bioethics, National Institutes of Health

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Our next speaker -- our first speaker today -- is Dr. Ezekiel Emanuel. Zeke was one of the driving forces behind this effort while he was working at the White House last year.

Dr. Emanuel is the former head of the department of bioethics at the clinical center of the National Institutes of Health, and he is an oncologist who also has a Ph.D. in a field that is dear to me as well, political philosophy. Dr. Emanuel has published widely on the ethics of clinical research, health care reform, international research ethics, end of life care issues, euthanasia, the ethics of managed care, and the physician-patient relationship.

Dr. Emanuel previously served on President Clinton's health care task force, the National Bioethics Advisory Committee, and on the bioethics panel of the Pan American Health Care Organization. As of September 1st, Dr. Emanuel will be the Robert and Diane Levy University Professor at the University of Pennsylvania, and the chair of the -- of Penn's Medical Ethics and Health Policy department, and Vice Provost

for Global Initiatives.

Welcome, Zeke.

DR. EMANUEL: Thank you. I am going to stand, if you don't mind. My high school debate coach would kill me for sitting and talking.

So, I'm here to talk about the ANPRM, which was developed and then published this July. So let's see if I can handle all this. Just want to go through a brief history to remind you of where we've been, and also where the regulations that currently exist came from.

Many of -- you know the famous Beecher article in the New England Journal highlighting 22 scandals, if you will, in research at leading universities, then the release of the 19 -- the Tuskegee scandal in 1972, leading to the national commission, one of your predecessors, which published its final report, the Belmont Report, establishing an ethical framework for human subjects protections, leading to HHS adopting regulations for itself. Those regulations, after 10 years, being adopted by 14 agencies -- or part A of those regulations being adopted by 14 agencies.

So, let me just emphasize, first of all, that 10-year gap takes a long time to get a lot of agencies to work together to adopt regulations. Second, it's only 14 agencies, it's not all of the Federal Government, as many of us think it should be.

There are -- after 30 years of seeing this in action, as it were, a lot of problems have been identified with the Common Rule and the regulation: inadequate IRB time devoted to review of high-risk studies; time-consuming reviews of -- and continuing reviews of low-risk or no-risk research; such as surveys; inconsistent IRB practices regarding research with biospecimens, claims data, medical records data -- a lot of this pre-existing data has been a problem; multiple reviews of multi-center trials.

Many of us have had the experience of spending basically a whole year of getting our protocols approved before we can start, because we're going through a number of different institutions, and there is no evidence that it reduces the risk or enhances the protections -- as a matter of fact, a lot of evidence that it doesn't.

Informed consent documents that we know, over time, become longer and longer, and written at a very high grade level, where the boiler plate actually tends to be the worst part of it. Lack of data. We simply don't know a lot of data about the actual risks of research. We see scandals, or we see something bad happening, and we have no context to put it into.

And then we have increasing evidence of what I will call -- probably contentiously, a little bit -- evasion of IRB review by a lot of people trying to say what they are doing is not research, so that they can avoid what is increasingly seen as an onerous process.

When we convened an interagency working group to examine this and see if we could actually reform the system, we had two goals. One was to enhance the protection of research participants, and the other was to improve the efficiency of the review process. We did not view these as contradictory. In fact, we viewed these as synergistic. If you actually improve the efficiency, you could spend more time on the really risk stuff, so that you could actually enhance

protections.

I am going to go through some of the specific reforms, to give people a sense. This may be the most important, which is to get a risk-based review process. The Institute of Medicine had a group about a decade ago look at the oversight process, and recommended a risk-based review process, although didn't flesh it out.

Here we've tried to flesh it out in the ANPRM, suggesting that greater-than-minimal risk research basically received the current protections, which is full IRB review, annual review. However, getting rid of the annual review when all you're doing is sort of standard clinical follow-up, or analyzing the data.

Things that are less than -- are minimal risk or less -- that is, they're no more risky than everyday life, which itself is somewhat risky -- you get expedited review by one person with the option to send to full IRB review, if for some reason that person thinks this is -- needs more attention -- and no annual review, again, unless explicitly justified, because it's going to be risky.

And then there is a lot of research which is only what we call information risk research. That is, unauthorized disclosure is where the risk is. That research would not have an IRB review, but would have to follow standardized data security measures loosely based upon HIPAA kind of measures is the proposal. And the idea there is you're not actually exposing people to physical or psychological risks, and that you -- having standardized data security -- is the best way to protect people from information risk.

So, surveys, focus groups, interviews, maybe economic and psychological studies with mentally competent adults would be excused from IRB review as a result, because it's really only information risk, but adhere to strict data security standards. Research, therefore, based on secondary use of existing data -- which, again, doesn't have any -- expose people to physical or psychological risk, would qualify for this excused status, which is a new status.

Written consent would be required for all uses of biospecimens with identifiers or without identifiers because, in our view, all biospecimens in the near

future are going to become identifiable with either existing technology or soon-to-be-developed technology. So the distinction there between identifiable and not, I think, really has to go away.

And consent would be a sort of standardized, general, open-ended consent, not a check box, complicated check box, and not for each specific use, which would be obtained at the time of admission to a hospital or clinic is the proposal.

Specific reforms would include also -- multi-site research would get only one IRB of record. You wouldn't have to go to 80, or 100, or 120. And institutions would obviously have to decide whether they want to participate in a protocol, but that's different than getting an IRB review.

One of the things we've identified is the fact that the minimal risk interventions that determine what's minimal risk and can get expedited review actually hasn't been updated in over a decade -- in 13 years to be specific. And so the proposal is to stand up a federal committee that would regularly update these minimal risk interventions, based upon data

submitted or data in the literature, so that you actually have a learning process that would be constant and dynamic to reflect actual risk.

Almost everyone who has commented on human subjects research protections has pointed out that, you know, the rules apply only to that stuff which is federally funded or going for FDA approval. There is lots of research that is not covered by these regulations, people bemoan that. Actually, to cover that would require legislation by Congress. You can tell me how likely you think that is.

But in lieu of that, you could actually require institutions to have all their research, whether federally funded or not, going for FDA approval or not, fall under the Common Rule. Now, that wouldn't -- still wouldn't get the entire universe, but it would get pretty close to the entire universe. It's a regulatory way of trying to achieve the goal, incrementally.

We have also proposed an electronic adverse event reporting system to develop a web-based reporting system that would permit constant input of information

on research that is being conducted. So we would actually have systematic and pretty comprehensive data on adverse events that would allow us to identify which research actually is low-risk, contrary to expectations, and which research may be hot spots of risk that we probably need to spend more time and attention with.

Right now, all we have on that is your gut reaction and my gut reaction, which is worthless, in my opinion. So we really do need to have a constant way of collecting this kind of data.

There is also several suggestions related to improving the informed consent documents to having explicit delineation of information that must be in documents, creating more standardized templates at the Federal Government level, so that people can be sure of what would qualify, and having all consent for adults who participate in surveys, focus groups, and similar types of research, because, after all, their answers suggest consent. And if you don't get their answers, you don't get data. So this seems like one of the areas we can both streamline and increase protections.

Standardized protection for information risk. Right now IRBs decide how data security is going to be done. Typically, they're not composed of experts in information technology and data security. So the proposal is to require institutions to implement HIPAA-like data security standards for research, posing only information risks, so that everyone knows what the rules are. This should also facilitate the exchange of samples, the exchange of data, because everyone will be under the same regime.

This comes to, I think, the reason I was invited, which is what can the Presidential Commission add?

So, here is a -- I will be very frank. Here is my warning to you. I have two warnings. The first is whenever there is a call for a response to a problem or a scandal like the Guatemala situation, there is a tendency to just add more regulations, another layer. "We're being tough." "Here is increased requirements." I think this is part of the way we get burdensome, inefficient regulations that end up not really protecting people, but sort of satisfy a one-day need

for a headline of, "We're Doing More."

I think the correct response is to reevaluate the whole package of protections to see what's helpful, what's unnecessarily burdensome, and actually, where we can make good, productive changes.

So, I think one thing that would be helpful is for the commission to look at the ANPRM and endorse the need to reevaluate existing regulations in general, and then to go through and maybe take some stands on some of the things that are in there, in particular, and add to -- given your experience now -- your voice to whatever you think is good, and maybe criticize what you don't think is good.

I would say the interagency group that I had chaired at OMB on the -- to develop the ANPRM, we recognized that we couldn't address all the issues that needed reform, that if we wanted to get something out, we had to be efficient and focused. And we explicitly set aside issues related to international research as something that we couldn't address in this time.

One area that we had raised and set aside, but thought really needed attention -- which I am going to

suggest to you -- is the area of equivalent protections. That is, when you go and look overseas at other countries and research conducted in other countries, there are provisions for countries that have equivalent protections for us to recognize those protections, and not impose our own regulations.

Here is my second warning. If you take up that suggestion, don't kick the ball down the road to a future committee, say, "Oh, someone should look at future protections, that's a really important area." You shouldn't simply identify it as an important area. Once, a long time ago, the IOM had another commission which sort of identified a number of -- was supposed to look at regulations or what needed change, identified a number, but didn't propose what the changes should be. We need the work. What will qualify as equivalent protection?

So, here is a suggestion, all right? Solve the problem. Delineate the principle or principles for determining what should qualify as equivalent protections to our Common Rule.

Specify what differences and regulations are

not ethically significant, we shouldn't worry about them; whether difference in continuing review time lines or processes for certification are necessary or different. Are they significant? Yes, they differ from ours, but are they ethically significant, or do they still provide equivalent protections?

Evaluate, in particular, whether certain current international regulations like ICH or the European Union's regulation offer these equivalent protections or not, or where slight changes would qualify as equivalent protections.

I'm not actually going to talk about this. Okay? So that's one suggestion, or two suggestions, I guess, for you.

DR. GUTMANN: Thank you very much. Before we engage in discussion of this, let me just say to everybody attending that our system of taking public comment would be if you have a question or a comment relevant to this or any other session, we have cards available. Please write your name and the question or comment down, and give it to any staff member here.

Will people who are members of the staff

please stand up, so -- there they are. So there are staff members in every corner. And feel free to write a question or comment and put it on, and they will deliver them up here, so we will know, and we will engage with those as our time permits.

Let me just -- let me begin, and then see what other members of the commission have to say. But actually, before I do that, what I didn't do yesterday, which I meant to do, was ask the members of the commission to introduce themselves. So, Anita, would you begin? And we will go around the table.

DR. ALLEN: Thank you, Amy. I am Anita Allen, professor of law at the University of Pennsylvania Law School.

DR. ARRAS: John Arras, professor of philosophy, University of Virginia.

DR. ATKINSON: Barbara Atkinson, executive vice chancellor and dean of medicine at the University of Kansas Medical Center.

DR. MICHAEL: Nelson Michael, director of the U.S. military HIV research program at the Walter Reed Army Institute of Research.

DR. FARAHANY: Nita Farahany, a professor of law and philosophy at Vanderbilt University.

DR. WAGNER: Jim Wagner, serving as president of Emory University.

MS. ALI: Hi. Lonnie Ali. I am a caregiver and an advocate for Parkinson's research.

DR. HAUSER: Steve Hauser, chair of neurology, UC San Francisco.

DR. GRADY: Christine Grady, the department of bioethics at the NIH Clinical Center.

DR. KUCHERLAPATI: Raju Kucherlapati, professor of genetics and medicine at Harvard Medical School.

DR. GUTMANN: So, Zeke, you mentioned -- and we are all acutely aware of -- not only that there are many rules and versions of them in different agencies, but there is a lot of clinical research concerning human subjects that goes on, sponsored by different government agencies, and also privately sponsored.

One of your specific reforms is an electronic adverse event reporting system, which would be terrific, if, you know, we had it. The question I have

is, do we need, before you get an adverse event reporting system, an electronic system that enables us to know what experiments are going on with human subjects that are -- that's just sponsored by the U.S. Government.

We are engaged in an empirical background study because we've been asked to assure the President that these studies are sound. And there is no database for them. We know clinicaltrials.gov, but that doesn't -- it's not at all comprehensive.

DR. EMANUEL: I have certainly made this comment for, I think, the last 15 years, that I think it's a scandal that neither the head of the FDA nor the head of the NIH can actually report how many people are on clinical research trials sponsored, how many people have had an adverse event, and tragically, how many people may have died, or any other relevant piece of data.

I actually -- so my view of the adverse event reporting system is actually that it would do both. You would actually know how many people are enrolled in -- depending on how you create that -- phase one,

two, three clinical research trials, if you want to add observational studies and other things which are low risk. You could. But at least on those trials -- so we would both know who is on and have a, therefore, a denominator. If you can have an adverse event reporting system, it will only produce meaningful data if you actually have a denominator. So you would actually have to have both, which is know how many people --

DR. GUTMANN: Right.

DR. EMANUEL: -- are enrolled. I have actually also --

DR. GUTMANN: That's precisely why I asked the --

DR. EMANUEL: Right, right.

DR. GUTMANN: -- this question. You have to have the denominator base.

DR. EMANUEL: Right, right.

DR. GUTMANN: Which is really, in this day and age, with computerized systems, should be on the order of easy from the scale of easy to hard to implement.

DR. EMANUEL: Well, I do think --

DR. GUTMANN: Right? It's much harder to do retrospectively than it is --

DR. EMANUEL: Right, in --

DR. GUTMANN: -- to do prospectively.

DR. EMANUEL: In fairness, because the enrollment is distributed in tens of thousands of places, in trials, it's not -- you actually have to oversee and get those people -- or have some requirement for them to actually introduce the data in a common format, et cetera. But I agree with you, given the fact that we do have the Web, and it should be relatively easy.

Fortunately, the other thing is six federal agencies, including the NIH, FDA, OHRP, the VA, and DoD, have pioneered a template called the Basel Adverse Event Reporting System, which is now being beta tested related to genetic -- gene therapy studies, which I think is a good platform that we can build on.

So, for a long time I have agreed with that statement.

DR. GUTMANN: So it's doable?

DR. EMANUEL: I think it's doable. I mean

it's not going to be free, like everything. But the question is, isn't that a sort of -- it's the sort of basic amount of data you need to really analyze the system and its safety.

DR. GUTMANN: Correct.

DR. EMANUEL: And then I think we'll find out.

DR. GUTMANN: Correct, correct.

DR. EMANUEL: How safe is the system, and also, where do we focus the resources to make it safer?

DR. GUTMANN: Correct.

DR. EMANUEL: And where can we sort of, as it were, not have to spend a lot of resources, because it already is safe, and it's not going to be a problem, and we can target the limited resources in a more effective manner for protecting people.

DR. GUTMANN: Thank you. Jim?

DR. WAGNER: Zeke, thanks for the presentation and overview -- very clear -- about where we hope to go with these reforms. And I appreciate also the two suggested charges for the commission to offer an opinion on.

I was imagining that you might ask also our

opinion, or for us to say something about the notion that the Common Rule or the revised Common Rule might be applicable to non-federally-funded research, as well.

As I contemplate that challenge, I wonder what is being thought about. What do others imagine the -- anticipate that the mechanisms of accountability would be for the Federal Government to try to impose the common rule on research that they, themselves, are not supporting?

DR. EMANUEL: Well, I mean there is a -- I would presume you could create a situation where there are a whole series of penalties that aren't just, you know, turning off the federal money spigot, which is the sort of common penalty at the moment, suspending your ability to --

DR. WAGNER: So essentially, a criminal mechanism?

DR. EMANUEL: Well, it could be, I presume, civil fines, as well as criminal penalties. I'm not an expert, I'm not a lawyer in how you might -- you know, the administrative law of this. But we have lots of

other, you know, either financial or other penalties that people -- could be imposed upon institutions, so --

DR. WAGNER: It was a financial category that I was hoping you had some creative thoughts about, because obviously that's the mechanism that we have for those that are federally funded. And even for institutions like universities who may be performing work that's not directly federally funded, but owing to the fact that we are under -- you know, that we have large amounts of federal funding, I see good ways to put teeth into the universities.

But into private institutions --

DR. EMANUEL: Well, look. I think fines are possible. So a large category which don't receive federal funds are sort of IVF clinics, which, because they're involved in reproduction, tend to fall outside of almost all our regulations, because we can't agree on what should happen there.

DR. WAGNER: Good point.

DR. EMANUEL: So that would be a case, it seems to me, of where you might have sort of civil

monetary penalties imposed.

DR. WAGNER: So, in your view, we shouldn't hesitate to make some recommendation about broader applicability of the revised Common Rule, simply because we anticipate it would be difficult to enforce? You feel there is mechanisms -- your opinion --

DR. EMANUEL: Yeah, I guess if I were hesitant on that, it would mostly be because it would involve legislation, and I just want to be practical. Let's do what we can do, and let's not sort of --

DR. WAGNER: So --

DR. EMANUEL: -- windmills, which just aren't likely to happen. I mean that call has been out there for decades and, you know, just not going anywhere. We should be more practical, and let's get important work done that we -- that is within our purview.

DR. WAGNER: Thanks.

DR. GUTMANN: Raju?

DR. KUCHERLAPATI: Thank you very much. You know, when the commission was thinking about, you know, the kinds of topics that it wanted to examine, and I think when we talked with colleagues, this was a very

important issue to try to reexamine the Common Rule, so I would greatly

appreciate the efforts that you have described ongoing.

The question that I have is that to -- many people argue that to improve human health, that you need to use humans more as experimental organisms. And if that is, indeed, the case -- I don't mean it in a bad way, but in a good way -- that if we were to do that, that means that, you know, we're going to have a lot more humans participating in these types of studies.

Do you think that we have adequate amount of infrastructure to be able to handle that, or that these new proposed rules would be able to deal with that increased number of individuals who might wish to participate in these types of studies?

DR. EMANUEL: Well, that's probably well beyond my expertise, but let me say it never stopped me from making comments before.

So let me just say a lot of it depends upon the kind of research you have in mind. Some of it is much more intensive in the laboratory. Some of it is observational, some of it is more epidemiological, and

sort of scaling it up and scaling it down
is -- requires less bricks and mortar, as it were. And
the infrastructure, I think, is available.

So, I am less concerned about the -- you know,
do we have the capacity, it seems to me, than I am
about can we make the oversight both better and more
efficient.

I mean one of the things that I think strikes
many people is if you have a relatively large
multi-centers trial, getting it from sort of
protocol-written to running is probably a two-year
process. That seems crazy, from all sorts of
standpoints. It's a waste of money, it's a waste of
science, since, by the time you get it up and running
you may be behind the curve. And it seems to me that
it doesn't -- that two years is probably not adding to
protections. And that is, I think, what -- in my view,
that is the biggest lesion we have.

DR. GUTMANN: Yeah. Nita?

DR. FARAHANY: Thank you for the presentation
on this. I am grateful for all of the work that you've
done on streamlining, particularly the Common Rule and

the recommendations for doing so. A lot of what we've heard is that many of the regulations, as they exist, are quite cumbersome and difficult to comply with, and I think bringing it in line with the rationale for protection, particularly in areas like creating exceptions for surveys makes tremendous sense.

One of the things that we have heard a lot and been struggling with ourselves is thinking about how do you make the ethics requirements actual -- not just, you know, check-boxes that people sign off on, but how people actually understand that they are designed to protect human subjects, such that researchers are actually seeking to do that, rather than just check off boxes. It seems like some of the revisions that you're suggesting helps to do that by getting rid of regulations where it doesn't make sense.

But how do you ensure that those regulations that do exist, particularly when you extend it to new institutions, becomes more than just a check-box, and instead, really a consideration by researchers about how to ensure the protection of human research subjects?

DR. EMANUEL: So you're getting into human psychology and institutional design, another area I have no expertise in, but it will not prevent me from making more comments.

So, the first thing is I do think we have entered what, what in my view, is a dangerous place, which is increasingly I do think researchers view this -- two things -- first, as an onerous hurdle to get over, and therefore the check-box mentality comes more into play, especially if they can't see the rationale between what they're doing the research on and the regulations.

And so, I do think actually, ironically, slimming down the -- or not slimming down, but focusing the full IRB review on those things which are truly greater than minimal risk is actually going to help with compliance. You will also, therefore, I think, see less of the attempts to contort things and say, "Well, it's not really research, this is other kinds of work quality improvement," or whatever, so I can evade the rules. And so, I do think that, in and of itself, is going to be helpful.

The other thing which I find, from both

teaching researchers a lot in this area and just talking to them, is the rationale for why they're supposed to do this is disconnected from what they're supposed to do. And so, if you don't have a good justification -- I mean these are really relatively intelligent people. This isn't their everyday world, but they do understand justifications, and they do understand, yes, if I did this it would be better.

The problem is, we have a situation where, if I did this, it's either not going to be better, or going to be worse, and it's going to make my life hell. So, I think that is a problem, and leads to a certain kind of disrespect for the rule.

So, I think if we actually connect the justification with the protections, that will help, itself, in establishing - is that a problem?

DR. WAGNER: No, I just wanted -- real quickly to that point, we were having this conversation about ensuring -- trying to reconcile the divorce between regulation and rationale. And it seems that -- I hope what I hear you saying is that both parties need to be modified to mend this marriage.

In other words, simply to reinsert the rationale around each of the tic marks just makes for more reading, and no less onerous responsibility.

DR. EMANUEL: Right, right.

DR. WAGNER: But rather, that both sides need to be revised, the number of tic marks and what they really amount to, in terms of a pledge that says, "I am satisfying a particular rationale," as opposed to many, many, many tic marks that ensure that you don't have to think.

DR. EMANUEL: Right, right.

DR. WAGNER: Or are intended to ensure that you don't have to think about the rationale, because someone else has imagined that if you check all those properly, you are in compliance.

DR. EMANUEL: Well, I agree with you. In general, I don't think most clinical researchers are sort of -- malicious people who just try to get rid of -- I mean if they are evading rules, you have to think there must be some reason that normally otherwise pretty good people who do the right thing most of the time are really trying to get around this. And that

has to be that this makes no sense to them, and is really looking like it's just trying to impede them for no good reason. That is a bad place to be, I think, institutionally. Right, right. You have to -- right, you have to change the rule.

And so, I do think that, to those people who say, "Well, we can do all this under the current regs," I actually think that's -- first of all, I think it's wrong; you cannot change the defaults.

Part of what the ANPRM is trying to do is to change the defaults. The default of a survey is you will get oral consent by people actually answering your question, and you don't need an IRB, you can adhere to the data safety monitoring -- the data security rules. Or, if you're doing minimal risk, you get expedited review, and you fill out a shorter form. That change, I think, will help substantially, because people will understand how -- what they're doing is linked to how they're being regulated.

DR. GUTMANN: So, this is very helpful, because --

DR. EMANUEL: Sorry.

DR. GUTMANN: -- this is -- no, this is something that is a very important broad theme that we have heard over and over again. And we really, I think, along with the reforms you are proposing, need to recommend something quite broad with some specifics attached to it on how to make progress here.

Because we've been moving as, you know, science and medicine -- if you take what Raju said, we need more and more of this kind of research, and yet the spirit behind it of doing good and doing good in an ethical way is not being promulgated through the way our rules are.

Let me take -- we have three questions and comments from those in attendance here. And let me read them -- let me take them one at a time and see if -- most of them are directed at you, some of them are directed at the commission, but let me begin and you can reply.

This one is from Ruth Macklin, who is a professor, we all know, at Albert Einstein College of Medicine, a professor of bioethics. Ruth, would you stand up? There is Ruth Macklin. I will just

summarize it, so -- and Zeke can answer.

Some social science research has risks that fall between physical risks typical of drug studies, and mere informational risks. Examples include domestic violence, adolescents engaged in high-risk behavior, research involving people engaged in illegal activities -- for example, drug use, sex work. How do you -- and now I'm just -- how do you deal with that, given that you want to cordon off certain clinical trials for the more extensive -- this is a question that is -- you had to have thought about, because whenever you draw lines --

DR. EMANUEL: You see all this gray hair?

DR. GUTMANN: Yeah.

DR. EMANUEL: So, first of all, the ANPRM specifically asks this question, which is, "In the case of surveys and other psychological" -- where the main risks are psychological -- "how do you identify what would be greater than minimal risk in that sphere?" We don't think that there is a great example. That is the first thing.

The second thing is notice that I think I said

on the surveys focus group that you would not have to go through an IRB, or be excused from the IRB system under the new proposals. I think I restrict it to competent adults, and the ANPRM does restrict it to competent adults, and that is for a reason. You might want to have additional protections for children.

But in some cases we know that, for kids who are engaged in high-risk behaviors and other things, we do want to actually survey them. And the question is whether it's a higher risk not to have the information from them, or --

DR. GUTMANN: Yeah.

DR. EMANUEL: -- at better -- or that they're pretty savvy and will be able to differentiate whether they want to participate or not.

So I think, you know, one way -- place to start is let's say, for some -- maybe domestic violence, sex abuse, illegal behaviors, initially you're going to put it into the minimal risk but not greater than minimal risk category. It gets reviewed by a person, that person can decide whether it really needs full IRB review or not.

And then, by God, we'll be able to study this, and we'll have an adverse event reporting system, and we will understand whether we're getting a lot of adverse events or, in fact, whether this is actually, you know, really not that risky and people are participating.

DR. GUTMANN: When you say "a person," I assume you're going to ask for somebody who is independent of the equivalent of a, you know, of an IRB. In other words, the person is not going to be a person who is connected to the research itself.

DR. EMANUEL: So -- right. The idea is --

DR. GUTMANN: Because the whole --

DR. EMANUEL: Right.

DR. GUTMANN: I think the thrust behind this question is are you going to leave it just to the researchers themselves to determine this, and this -- the fact that you're asking for an expedited --

DR. EMANUEL: Can we go back to the slides for a sec?

So, one thing I probably didn't emphasize enough is this slide. So, in the greater-than-minimal

risk, you go to a full IRB review, which is the current system, basically, and you -- all that's being altered here is the annual review process. So when you're not actually exposing people to additional risks, you don't have to have a -- the minimal risk, you get reviewed by one trained person. Typically, that person is either an IRB member or someone in the protocol office, unrelated.

Now, in the information risk, the -- ANPRM suggests as a possibility for people to comment on, you would have a form that you would have to register with the IRB. You can imagine two possibilities: you register with the IRB and you can either start immediately; or, you give the IRB a week to sort of look at the form and say, "Hey, you know, we think that this should go into the -- either a full IRB review, or one trained person."

DR. GUTMANN: Good. Okay. For Zeke, this is from Roger Glass, director, NIH Fogarty Center. Many companies are taking their clinical trials overseas to avoid regulation, scrutiny, and ethical issues, such as paying high fees for doctors to recruit patients. Much

of this data remains unpublished, especially if it's -- now my -- I don't know whether to blame the handwriting or my ability to read it, or -- oh, sure. Especially if its results are negative or if adverse events occur. How does a Common Rule reform affect this form of research?

DR. EMANUEL: Well, if in fact --

DR. GUTMANN: Roger, would you please stand up, so people -- there is Roger.

DR. EMANUEL: If, in fact, the companies are seeking FDA approval, typically they're going to have to register with the FDA. But again -- well, not again. This -- ANPRM may not solve all problems in the entire universe of problems here, so it's -- I think we said we didn't tackle everything, that's why we didn't do equivalent protections and other things.

So, I think there could be problems, and especially, you know, if people are intent on evading reporting and releasing data, there is going to be -- it's going to be really hard to enforce. You're not going to develop rules for that problem. So it's a problem which revision of the regulations is not going

to solve, it seems to me.

On the other hand, if they are planning to go to the FDA, they are going to have to register and use the --

DR. GUTMANN: Yeah.

DR. EMANUEL: -- God willing, the adverse event reporting system.

DR. GUTMANN: Yeah. The third question I'm going to say is from Joseph Millum of the NIH, and it's about equivalent protections. And I'm going to save it for the next session. Joseph, just stand up so I can see where you are. Joseph, we will get back to this when Christine and Nelson speak, because it's actually directed to the commission. So we will hold off.

I'm going to take two quick comments or questions, and we're going to eat into our later break. Anita and John?

DR. ALLEN: I have a question for you, Zeke, about your recommendations regarding lightening the IRB requirements for multi-site research. I understand the problem. It seems absurd, in a way, to have 25 different IRBs looking at the same research protocol.

But I'm a little bit concerned about what we might call IRB shopping. Not all IRBs are created equally. There is tremendous variation in quality and composition. Isn't there a risk if we limit the need for IRB oversight to, say, one IRB for a multi-site project, that we will have some pernicious IRB shopping, and the researchers will look for the easiest IRB to get through, the quickest ones, and not necessarily the best ones?

DR. EMANUEL: I would have thought that was the problem today, when you want to get through -- you have to get through 100, so you're looking for the easiest ones. But the ANPRM does ask about how to limit IRB shopping, and actually has several proposals or suggestions for how you might identify which IRB you would have to go through.

So, we could consider the following. You have to go through a national IRB, like the NCI's national IRB for cancer, multi-center cancer trials. Another possibility is you have to go to the IRB for the PI, the principal investigator, so that, you know, you would be choosing your principal

investigator -- presumably that's on scientific expertise, and not on who their IRB is. But maybe there is another good suggestion you have that could be added there. I think this is not a trivial problem, but I do also think that there are some reasonable solutions.

Let me also say I think the other problem is that, as much as this is commented on, let me just say industry has a very big reason not to sort of stint on this. Because if something goes bad, and they have been seen to do a malicious thing like trying to skirt the system, they're going to lose hundreds of millions of dollars. So they're not into that game. And I think most clinical investigators, it's the IRB of their home institution that they're going to. And under this system, you know, presumably they'll have more time to focus on the really high-risk research.

And so -- and since you're only going through one, you're not going to be wasting so much time in others. So I think the incentive to sort of evade is going to actually go down, rather than up.

DR. GUTMANN: John?

DR. ARRAS: Yeah. Zeke, thanks for a really helpful presentation. I really do appreciate the drive toward simplification, but I am wondering if it might extend a bit far in one area that I can think of, which is the area of kind of blanket generic consent for research on tissue samples, right?

So, you know, we have some case studies out there where people gave consent to study their samples. The Havasupai Tribe comes to mind as an interesting case study, where they gave consent for, I believe it was, diabetes research. And then researchers turned their attention to the linkages between this tribe's DNA and psychiatric conditions.

How would your approach deal with a case like that?

DR. EMANUEL: What -- I mean I don't understand what the dilemma is here. The researchers collected under one rubric, and then they bait and switched to do a different kind of research. That's not permitted.

Now, if you --

DR. ARRAS: Okay --

DR. EMANUEL: So, here is what the tribe -- they don't want their stuff done for general research. Guess what? They don't sign that piece of paper, and they don't give their consent. It's just the old, normal way.

It seems to me, in that case -- I don't actually understand all the hoopla about that case, to be honest, in the following sense. They didn't actually consent for the research that was done, as I understand it. I'm not an expert in the case. They consented to diabetes research. This wasn't diabetes research. Guess what? Didn't qualify.

DR. ARRAS: Okay. So then I guess --

DR. EMANUEL: In the new system there will be a form. You don't want your stuff used for other research, you don't have to sign the form.

DR. ARRAS: Oh, okay. No -- so when you said there would be a kind of generic consent form --

DR. EMANUEL: It's not required consent.

DR. ARRAS: -- I just sort of assumed that would mean that you gave permission for any and all kind of research in the future.

DR. EMANUEL: Yeah, you would. And if you didn't want any and all research done, you wouldn't sign that form. Right? It's amazing how that works. When you don't give your consent, you're not supposed to do it.

DR. ARRAS: Okay.

DR. EMANUEL: So, I mean, it seems to me that the Native American tribes that are worried about their samples being used for something that they didn't authorize, you're right, it ought not to be used for something they didn't authorize. And this is giving them an opportunity.

What we know from the data that's been -- you know, now there are thousands and thousands, tens of thousands of people, who have actually answered questions on this. In general, where "in general" means 80 to 90 percent of Americans, want their samples to be used for research, what they want to be asked is, "Will you use it for research or not?" They don't want to be asked, "Which lab is going to do it, which disease is going to do it," and all that other stuff that had been suggested for the -- lo, these 15 years.

That's what this ANPRM -- it's actually listening to what people say in their mind is important consent, and trying to put it into practice. If you don't want your sample used for determining who your ancestors were, there is a real simple thing. Just don't agree to it.

DR. ARRAS: Okay.

DR. EMANUEL: That's what the word "consent" is. It's not trying to take away consent, it's trying to say, "This is what the consent is going to cover."

DR. GUTMANN: Zeke, thank you very much.

DR. EMANUEL: No problem.

DR. GUTMANN: It was very helpful, thank you.

(Applause.)