



**Presidential Commission**  
*for the Study of Bioethical Issues*

## **TRANSCRIPT**

**Amy Gutmann, Ph.D.**  
Commission Chair

**James Wagner, Ph.D.**  
Commission Vice-Chair

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DR. GUTMANN: I would love to welcome everybody. I'm Amy Gutmann. I'm president of the University of Pennsylvania, and I have the privilege of chairing the Presidential Commission for the Study of Bioethical Issues. On behalf of myself and our vice chair, Jim Wagner, who is the president of Emory University, I'd like to welcome you to our 20th meeting.

Let me begin by noting the presence of our designated federal official who is also Bioethics Commission executive director, Lisa M. Lee. Lisa, please stand so we know who you are. We all do, the commission members.

And I'd also like our commission members to go around and introduce themselves. Let me begin with Anita.

DR. ALLEN: Thank you. I'm Anita Allen. I'm vice provost for faculty at the University of Pennsylvania and professor of law and philosophy.

DR. MICHAEL: I'm Nelson Michael. I direct the U.S. military HIV research program at the Walter Reed Army Institute of Research.

DR. GRADY: Christine Grady at the department of bioethics at the NIH [National Institutes of Health] clinical center.

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

DR. KUCHERLAPATI: I'm Raju Kucherlapati. I'm a professor of genetics and medicine at Harvard Medical School.

DR. SULMASY: Dan Sulmasy, the department of medicine and Divinity School at the University of Chicago.

DR. ATKINSON: Barbara Atkinson, the planning dean for a new school of medicine at University of Nevada Las Vegas.

DR. GUTMANN: And is Nita Farahany on the phone? Not yet. Well, Nita is sorry she can't be here, but not too sorry because she just delivered a wonderful, young -- obviously, young member -- a wonderful little girl into the world, she and her husband, named Estrella. Otherwise will be known as Ella. So we all congratulate Nita, and she may be on the phone later in our meetings.

I'm going to say a few words of introduction and then ask Jim to say a few words. We have a lot of work to do in this one and a half days.

As an advisory body to the President of the United States, our commission considers ethical issues with a particular focus on U.S. perspectives and policies. But it's been the case for many, many decades and it's only gotten more evident that bioethical issues are global in their nature and in their reach.

And you can see that just by looking at U.S. global engagement and its implications in relations to a variety of health, science and technology-related ethical concerns. The most obvious is the Ebola epidemic which affected our country after it affected very seriously and is still affecting three countries in west Africa.

The ability to distinguish between our -- what's in our nation's interest and what's in the interests of the world is increasingly difficult and perhaps a futile exercise in the case of bioethical issues of health. We have turned our attention, beginning at our November meeting in Salt Lake City, to U.S. engagement to the global response to the current Ebola epidemic, and we focused on what lessons might be learned from recent U.S. response to Ebola at home and abroad.

And today, the Commission has asked speakers to focus on three particular issues in the context of the U.S. response to the current Ebola epidemic: quarantine and travel monitoring and restrictions, randomized controlled trials and the collection, use and international sharing of bio specimens for research.

It's really those issues are front and center. There are many other issues. We acknowledge that robust and reflective deliberation about complex ethical challenges in public health emergencies is not best done in the midst of an epidemic. That is, the whole point of deliberation and education is to prepare us for confronting epidemics speedily, the way they must optimally be confronted.

It's not that one stops deliberating, but one does pause for a moment and act very quickly. Deliberation is about discussion and action. It's not just discussion. But to deliberate, to begin deliberating when there is an epidemic is the worst possible way of engaging in deliberation other than not engaging it at all.

So the purpose of our commission is to think, deliberate and issue a set of recommendations for how we can best learn from what we did well and what we did not so well in a serious crisis situation.

By the way, the crisis is not over. I was pleased to see that the front page of *The Washington Post* is continuing to cover what is happening with Ebola, and I couldn't help but think that even though it subsided in Sierra Leone, Liberia and Guinea, the three west African countries which have been hardest hit by far, if any three states in the United States had the ongoing incidence of Ebola that those three countries now have, we would still be in crisis mode.

So given the global nature of ethics and the global nature of the Ebola crisis, we are still facing a crisis.

Not to mention, which we can in our deliberations, measles in the United States which underlines the importance of education and deliberation in an ongoing way that one can never take for granted protections. And when one does and thinks that vaccines which are effective are no longer necessary for a subgroup, that's a problem.

So we need to continue to think about that as well.

I believe that the overarching theme of all these discussions is that major infectious disease epidemics are a matter of U.S. concern for both ethical and prudential reasons. We are obligated to engage in such devastating outbreaks from a global justice perspective, and we're also considering the ability of infectious diseases to travel in our interconnected world. It is prudent for us as a country to address epidemics at their source.

It is therefore both in our humanitarian and our national interests not to wait until diseases come to our shores before we begin, and in the case of Ebola, continue to address how best to respond to them as we're doing today. A very important theme is that we as a country and we as professionals and we as a public best respond in partnerships with others.

And now returning to today's meeting, I want to take -- and then I'll it over to Jim to say a few words. I just wanted to preface that as a framework for how we have been as a commission deliberating and we have actually -- will spend more time doing so and extremely fortunate to have a group of distinguished guests to present to us today.

I want to take just a moment to explain how we will take public comments. At the registration table, there are comment cards, but also bioethics staff members here in the room have comment cards as well. And I always like to recognize our fabulous staff, so would you all stand up and hold up your cards.

So anyone who wants a card, just -- there are lots of people here within one or two people of you. Just ask for a card, write down your comment or question. Somebody will pass it up to Jim or myself, and as long as we have time, we'll take them. And if we don't have time, we will get back to you and answer them one way or the other.

So thank you all in advance for participating in our discussion, and now our vice chair Jim Wagner.

Jim, would you say a few words?

DR. WAGNER: And a very few words. First of all, to commissioners, welcome, it's good to be working with you again.

To guests, those right before us and those who will be following you, welcome. It's good to have you here.

I want to reiterate your two big points, points about timing and points about scope. That with regard to timing, it is important to deliberate, not just during a health emergency but to do so ahead of time.

Ebola does indeed give us a highly visible, if not currently the most lethal, but highly visible example from which to capture public interest, capture our own interest, capture government agency interest in order that we might adopt better practices for timing about our deliberations and preparation for health emergencies.

And the second point you make is scope. We are very comfortable with the words “public health” and “global health,” but I think our minds imagine that there must therefore exist something else called “local health.” And, in fact, at least with regard to communicable diseases, it may be that there is no such thing as local health. And if we’re going to pay attention to ensuring our local health, it will require that we look globally and act globally.

Last points I want to make, I was given some statistics. This is our 20th public meeting since the commission was established by President Obama back in November of ‘09. We’ve met quarterly all around the country to discuss and deliberate on topics we’ve chosen, topics we’ve been assigned.

We’ve heard from exceptional speakers. In fact, something over 200 speakers from around the world have come to advise us, and they have provided the commission with the critical background, the information, the insights that have helped us form all of these recommendations.

And you guys, we guys I guess, have deliberated more than 135 hours in public, anyway. Actually, our formal deliberations have to be in public, as required. We do swap some email conversation around in the off time as well, and there’s enormous work. The staff neglected to put in the equal or larger number of hours that they themselves put into this list, so we want to thank you and applaud you as well.

And with that, I think it’s appropriate to get on with Meeting 20. Thank you very much.

DR. GUTMANN: Thank you.

## SESSION 1: ETHICAL ISSUES ASSOCIATED WITH RESEARCH IN THE CONTEXT OF A PUBLIC HEALTH EMERGENCY

DR. GUTMANN: Well, we have a terrific panel to kick us off, and I'd like to begin with one introduction at a time and then ask each of our panelists to say a few words and after each of the panelists presents, we'll then open it for commission and public discussion.

We're going to begin with a panel on ethical issues associated with research in the context of a public health emergency. Our first speaker on the topic is Dr. Clement Adebamowo.

Did I get -- will you pronounce it for me, your last name?

DR. ADEBAMOWO: Adebamowo.

DR. GUTMANN: Adebamowo. Who is currently a professor of epidemiology and public health at the University of Maryland School of Medicine and adjunct associate professor at the Harvard School of Public Health in Nigeria -- at the Harvard School of Public Health.

In Nigeria, he holds appointments -- there is no Harvard Public Health -- yes. In Nigeria, he holds appointments as a research scientist at the Institute of Human Virology, director of the Center for Bioethics and chairman of the National Health Research Ethics Committee.

So our first speaker could not be more well suited to kick us off on this topic. He is the principal investigator for several training and research grants and contracts, including the West African Bioethics Training Program.

He directs an NIH-funded African collaborative center for microbiome and genomics research in Abuja, Nigeria. His research interests span research, ethics, cancer prevention and management, obesity, diabetes and metabolic syndrome and nutrition epidemiology.

He's a member of the Expert Advisory Panel on Clinical Practice Guidelines in Research Methods and Ethics of the World Health Organization and is also editor in chief of the *Bioethics* online journal.

Welcome and thank you for being with us.

DR. ADEBAMOWO: Thank you very much, and I first want to appreciate the commission for the tremendous work that they have been doing over the past several years. And in recent times, quite a few of the materials that the commission has put out on bioethics education has formed an important part of our curriculum in the West African Bioethics Training Program, so thank you very much.

So I'm going to speak briefly on the ethical issues, as she said, research in the context of public health emergency. And as a Nigerian, this is something that we have both current and historical experience with, and the experience that we've had to a certain degree does inform the current attitudes and practices that we have towards these kinds of emergencies and how we are training our national health system to respond.

So as many are aware, in 1996, we witnessed what was the largest cerebrospinal meningitis epidemic in west Africa, affected millions of people with about 300,000 deaths. At some point in the epidemic, we were receiving about 300 new cases per day at one of the centers.

And during this epidemic, there was an attempt at a clinical trial that then had all these fallouts, and those events informed the government, the people and the Ministry of Health in planning ahead to respond in case we have similar events in the future.

So it wasn't particularly surprising that come Ebola, the National Health Research Ethics Committee of Nigeria was very much involved as one of the tripod that the government set up to advise and implement a response.

In Nigeria, we had 20 cases, eight fatalities, and we seem to have by and large contained the epidemic. So what did we think about, and why did we think about them?

Well, we have absolutely no doubt that modern clinical drug and medical and public health response is a common patrimony for all mankind. It's something that through debate, research, investment and the sweat of a lot of people we have come to arrive at certain common principles, and it's not likely that we are going to step back from those principles.

For example, we believe that modern drug development requires randomized clinical trial as the highest level of evidence that can be brought to bear on this discussion. We believe that modern research requires these principles of research ethics that we have learned and developed over the past several years.

But having said that, we also believe that these things should not be taken as doctrinaire positions that cannot be engaged with within certain circumstances and that we cannot adjust or reflect upon. And that as second part is why the Nigerian ethics committee at the beginning of the Ebola epidemic issued a guidance statement that said we're going to allow the use of therapies that have not completed the standard clinical trial development pathway in the context of this epidemic and share the data with all and sundry so that we can rapidly evaluate the efficacy of these interventions.

And so why did we take that decision? We took that decision first by considering the biological characteristics of the disease that we were dealing with and its natural history. Ebola, discovered in 1976, has been occurring in sporadic epidemics

affecting largely rural east African communities. And after causing some fatalities, it typically dies out.

So outside of the community involved in virology research, bioterrorism, it really had not grabbed worldwide attention in the way this current epidemic has. So at the beginning, there was major concern that this might be a different kind of Ebola.

We were also concerned that like any other viral epidemic, it will burn out, and we had no evidence that Ebola has an endemic variant within which we can take our time to conduct clinical trials and evaluate new treatments.

We were conscious of the fact that there were several treatments that were in the established phases of clinical trials drug development but had not advanced sufficiently to the level that we would ordinarily have just approved them going into human trials. And we were conscious of the absence of efficacious specific treatments for the infection.

With regards to our west African partners, the other countries in west Africa, we noted the rudimentary nature of the public health systems in those countries, that they were under-resourced and understaffed and that they lacked previous experience with Ebola just like we did.

The institutional and government response to the infection was slow and poor, and there were specific characteristics of the population affected in this instance that made us feel that we would really need to be dynamic in our approach to this disease. It's a largely young, rapidly growing, rapidly organizing population that's just recovering from years and decades of civil war and civil unrest.

This population was exerting tremendous psychological pressure on the surrounding environment and increasing their contact with wild animals and plants, and there was -- the population was marked by a high level of mistrust even within the population and between the population and its members and government agencies.

They also had a high level of belief in alternative medical systems and practices, and there were certain cultural practices that we thought might not be helpful in containing a spread of an acute infectious disease like Ebola.

Then we considered the international response which we judged as being slow and not well structured, not well organized. And we were conscious of the structural injustices and lack of equity within that international system, and we thought this must inform any decision that we make about how to respond to the disease.

And in so doing, we, of course, engaged the mass media and the modern social media, Twitter, Facebook and all that, and we knew these were going to play crucial roles.

So as part of the conversations we had then and subsequent conversations that I have had as a member of the World Health SITREP [situation reports] team response to the Ebola virus disease, we made certain recommendations and highlighted a couple of challenges. One of the recommendations that we made was the urgent need to continue to build local bioethics capacity because it was clear to us that our response was informed not only by our scientific background but also by being aware and knowledgeable about bioethical principles.

We thought it was important and recommended it's important to safeguard broad and equitable stakeholder representation at every stage of a response to an acute viral disease epidemic like Ebola. We believed that we need to think creatively about how international organizations should respond in future and how they need perhaps to do some internal review to look at what they did wrong and how things went so awry with the current epidemic.

Safeguarding and respectful handling of storage of biological samples were also thought to be very important.

Thank you very much.

DR. GUTMANN: Thank you very much.

Next we have Dr. Luciana Borio who serves as the assistant commissioner for counterterrorism policy and director of the office of counterterrorism and emerging threats in the office of the chief scientist of the FDA. In this capacity, she is responsible for providing leadership, coordination and oversight for FDA's national and global health security, counterterrorism and emerging threat portfolios.

Dr. Borio works in collaboration with other U.S. government agencies and internationally to define and prioritize requirements for medical countermeasures to respond to public health emergencies, coordinate research for accelerating their development and evaluation, set strategies for their deployment and use and facilitate access during public health emergencies.

She also leads FDA's medical countermeasure initiative which is a key component of a broad U.S. government program to improve the United States' capacity to respond quickly and effectively to public health emergencies. She was instrumental in coordinating FDA's response to 2009 H1N1 influenza pandemic and continues to coordinate FDA's preparedness and response activities for public health threats such as the ongoing Ebola epidemic.

Welcome, Dr. Borio.

DR. BORIO: Thank you. Good morning and thank you so much for the invitation. It's really an honor to be here and speak to you today.

So to me, at least, the framing of bioethical issues can be a conceptual exercise. As a physician, very concrete in my assessment of issues, and I think that examining the approaches really must take into consideration the facts about the disease and the facts about the available drugs, the pipeline.

And I think, as you know, we have taken a position that the best way forward to evaluate investigation of products in the pipeline for Ebola is to conduct an adaptive, randomized, concurrently controlled trial.

And by that, I mean a trial where patients are randomly assigned to the test drug and best available supportive care versus best available supportive care alone. And as soon as a test drug crosses a boundary, it is declared the winner and becomes incorporated into the background care of patients.

We think this is the most efficient and powerful method to assess a test drug's safety and efficacy. I have to say that we -- this assessment, this conclusion of ours, wasn't -- was borne out of extensive consultations with top experts at the NIH, at the FDA, at HHS, including those with substantial experience in alternative trial designs using the field, for example, of oncology or small trials. And these experts unanimously agreed that an adaptive randomized controlled trial was the best way to go.

And, of course, we also agreed that there were several alternative designs such as well-designed cluster randomized trials that are scientifically valid, but that those trials were logistically taxing, are much less efficient and may not have been feasible given what we knew about the drug supply. It wasn't a steady availability of drugs.

And we really put a weight into speed and efficiency because we felt that we only had a small window to study the investigation of products and to learn what helps and what hurts patients, and we were hoping to make a difference in this epidemic and if not for this epidemic, we wanted to make certain that we went into the next one with the knowledge to be able to take care of patients in the best possible way.

For alternative designs that rely on historical controls, I'll tell you unequivocally that in the case of Ebola, they are scientifically invalid. And to me, a scientifically invalid study by definition can't be ethical. And the reason I say that they are invalid is again because of what we know about the drugs and about what we know about this disease.

So we do not have good natural history data for Ebola, and the historical data that we have is a moving target. The historical data for Ebola shows tremendous variability in patients' outcomes, and moreover, mortality tends to decrease over the course of the epidemic. And we're seeing this now.

Also, as you know well, patients that are enrolled in a trial generally do better than patients who are not in a trial. So again, the results derived from historical

controlled trials are unreliable and misleading, and a drug that is erroneously thought to be effective because it seems better than the historical controls will compromise the development of truly effective drug. And future patients could be exposed to harmful or ineffective therapies, and worse, we wouldn't even be able to know.

There is an exception to the rule of historical controls. Some would argue that we could rely on historical controls if the treatment effect is so large to be unequivocal, if a therapeutic is called a home run. But then I ask you, which one are they referring to? Because at the FDA, we have tremendous knowledge of the pipeline, and frankly, I don't have any basis to identify a home run from the available pipeline.

So what we know about the drugs today for all the drugs in development, we truly do not know whether they will help or hurt. These are highly accelerated development programs, highly accelerated. So the products are not well characterized. We're able to move fast because we have a science-based agency with a tremendous flexibility in our framework, but again, these are not well-characterized products.

And given this tremendous uncertainty, to me, it's clear that we have clinical equipoise, and a design that can detect harm is really necessary to protect patient welfare.

So given these facts, I'd like to just talk a little bit about some myths that have emerged when debating trial designs. Some have asserted that patients in the U.S. survived because they received investigational product. It's not possible to attribute outcomes to investigational product that was used in the manner of emergency INDs and compassionate use -- and we do know that some Ebola patients do survive.

Patients in the U.S. received very aggressive supportive care that we think may have had an important impact on their outcomes. Some patients in the U.S. received investigational product were subsequently identified to have no activity against Ebola, so we can't really attribute those products to saving their lives.

I also heard that products with extensive safety data are safe and Ebola is a death sentence, so nothing can be -- something is better than nothing. We do have extensive safety data for some very toxic products. So we shouldn't confuse the availability of safety data with the product being safe. And some drugs can make Ebola worse, and we have to be really be careful about that.

The other myth I've heard is that a DSMB [data safety monitoring board] is in place and it will be able to detect harm no matter how poorly designed the study is, and as you know, that's not true, either. It is very challenging to detect harm in a single arm study of a very serious disease. They have little or no prospect of detecting harm.

And lastly, that RCTs [randomized controlled trials] are slow and can't be done in west Africa. The trial design developed by the NIH statisticians is very efficient. It affords tremendous economy of data collection, and because randomization is such a

powerful tool for generating comparable groups, very reliable conclusions can be drawn from those studies. In fact, the data derived is so strong that FDA has agreed that they would form the basis of approval.

And again, lastly, that west African countries won't accept an RCT. They have a tremendous history of conducting RCTs for very critical diseases. As you know, a randomized controlled trial just began in Liberia for vaccines. Volunteers are lining up to get this -- to enroll in this trial, and the government has expressed a strong interest in studying ZMapp as soon as the product becomes available in the coming weeks.

A number of health authorities at the ground have expressed a preference for properly designed informative trials such as RCTs rather than trials lacking scientific credibility and that are not able to detect harm to patients.

In my opinion and I'll be very frank, single arm studies with products that have no or little prospect of any benefit and known toxicity that have been undertaken already represent a complete abdication of responsibility of people in positions of power and influence. And eventually, this will lead to erosion of trust.

So to conclude, we have taken the position that the best way forward is an adaptive randomized controlled trial. We think it's the best way to protect patient safety now. We think it's critical for the future care of patients. We know that new Ebola outbreaks will happen, unfortunately, and we think that now is the time to do this right.

So thank you very much for having me here today.

DR. GUTMANN: Thank you very much.

Our last speaker for this panel is Dr. Nancy Kass, the Phoebe R. Berman professor of bioethics and public health in the department of health policy and management of Johns Hopkins Bloomberg School of Public Health. And Dr. Kass is also the deputy director for public health in the Berman Institute of Bioethics.

Dr. Kass conducts empirical work in bioethics and health policy and publishes primarily in the field of U.S. and international research ethics, HIV/AIDS ethics policy, public health ethics and the ethics of public health preparedness.

She is the director of the Fogarty Johns Hopkins Bioethics Training Program for African scientists, and Dr. Kass is an elected member of the Institutes of Medicine and a fellow of the Hastings Center. And from 2009 to '10 was based in Geneva, Switzerland where she was working with the WHO [World Health Organization] ethics review committee secretariat.

She has served as consultant to the President's Advisory Committee on Human Radiation Experiments, to the National Bioethics Advisory Commission and to the National Academy of Sciences.

Current research projects examine informed consent in randomized trials, ethics issues that arise in international health research and ethics in public health preparedness.

Welcome, Dr. Kass.

DR. KASS: Thank you very much. Thank you for inviting me. It's a pleasure to be here and take part in this discussion.

So what I'm going to do today is at the request of the staff, I'm going to have one slide on public health ethics. I want to be clear that we're talking mostly about research ethics and I get it that these are a little bit different and the public health ethics framework probably could apply at least as well to the measles response as to Ebola research, but I'm going to honor the request and spend a slide on that and then go on and talk about vaccines and treatments and maybe other things to think about in the research response.

So this is probably familiar to everybody, but I'm going to really quickly rehearse it. The point of a framework is to give us a structured way to think through an ethical problem. When the problem's not difficult, we don't need a framework. When there are competing views or even when some people believe there are competing views, like perhaps in the measles outbreak, it can be helpful to have a structured, disciplined way to think something through is, I guess, what I'll say about this.

So for me, that means asking six questions. The first is what is the goal of what the public health response might be and how much data are there to support it? What are the risks and burdens of it? How can they be minimized?

And then looking at the fairness implications and then when there is debate and disagreement, having some kind of fair procedure for navigating that. And obviously, things like a transparent meeting is a good example of that. And I would be happy to discuss that more, but I'm going to move on to research because that's our real agenda.

So I'm going to start by talking a little bit about vaccine trials, and I'm going to spend a bunch of time for both vaccines and treatment trials, talking about the placebo issue, but I want to raise just a couple other questions as well.

So these are some of the questions in my mind that come up when we think about ethics and vaccine trials. One question is who is the right target population, and the trial obviously that the NIH has launched is enormous and a lot of populations are going to be included which is great.

But particularly early on and if we think forward to other kinds of responses, it becomes a really challenging question sometimes to think through what's the right target population. There are populations we want to be able to target because

we believe rightly that we owe them certain kinds of protection like, for example, healthcare workers. They might not be the populations at greatest risk because of other protections they have in place, and it becomes important to think through this tension between those at greatest risk and those to whom we do owe very particular protections.

Placebo questions, what else must we be providing? The perennial tension, one of the perennial tensions in ethics and research which is the more you provide to protect the people separate from your experimental intervention, if you're successful, the less incidence you have, and how do you navigate that challenging one?

And should the target population for the trial be the same as the first in line for the rollout if it's successful? Generally, we say yes. It's an interesting question here.

So who's the right population? For healthcare workers, I guess I'll say obviously we have some kind of duty of reciprocity to help them here, people who are putting themselves on the front lines. A lot of people have gotten sick and died. My goodness, we have a duty to do everything we can to protect them, but again, this sort of nuanced, gray, problematic area between this instinct that is protective and sort of clinical and the need to mount as efficient a trial as possible.

A healthcare worker, one would assume, is in the best position to understand a placebo, to understand uncertainties, to understand the science behind it, but again, there may be a lower incidence rate among healthcare workers.

Household members of Ebola patients presumably are at pretty high risk, and unfortunately, in a normal household, there's little protective equipment. And so that obviously can be another target population.

Then this question of what is there a duty to provide. So let's hope that most healthcare workers in west Africa now have good personal protective equipment, but I think we all know that along the way, this has not always been true, particularly for local healthcare workers. And ensuring that that's available in the context of a trial is something to think about.

And then what about in households, what is there a duty to provide?

So let me move on to this question of placebo controlled and you may hear me say a few things that you heard Dr. Borio say, but I guess that's what happens when you invite a few people to prepare their remarks in advance. So I guess my first response to "should a trial be placebo controlled?" is it sounds like I'm being a snarky here, but I mean this as a genuine question. How else can we learn if the vaccines work?

And you'll see when I get to treatment trials, that I think that there sometimes are -- in my mind, I think there are a few options. For vaccine trials, I don't understand, at least the way I understand the epidemiology and incidence of this

disease, how else we could learn if the vaccines work.

There's no point in doing research if the question cannot be answered. One could make a policy decision to go out and roll out experimental things without knowing whether they work, but if you're going to do something that's called research, I don't understand it.

The placebo becomes particularly important where the incidence rates are so low. There's a whole bunch of other challenges that emerge, as everybody knows, when the incidence rates are as low as they are. It's the best public health news that we've gotten recently, that the incidence rates are low, but it obviously makes the research really challenging.

There's a whole other validity question. There was a piece in the *Lancet*, I think, this week about the baseline immunity of people who've been exposed, nothing to do with vaccine, that a lot of household members and some healthcare workers already show some signs of an immune response by virtue of being exposed. And is that something that we should build into a trial so that we don't confuse outcomes?

So let me move on to treatment trials and ask the same question about what the right design is ethically. Some say, and I think we've all been watching these debates, that it's unethical to deny a potentially lifesaving treatment to people who need it. The NIH trial, as we all know, is planned with a placebo based on this notion that we need -- that there's an ethical duty to figure out what works.

So this is again a classical ethical tension that people have -- thoughtful people have written about literally for decades -- it's the age old tension of a randomized trial where on the one hand, it is in our ethical and human best interest to have an efficient and valid trial where we learn as quickly as possible with methods we can rely on whether the experimental intervention works or not and this equally profoundly important need for us always to sustain in any kind of research that there are human beings behind it who are sick and desperately want and deserve whatever we know to be helpful and people who understandably want access the same way Kent Brantly wanted access.

So ethics is, in my view, and this is what I often say to my graduate students, it's not -- I don't feel like we as ethicists do our job if we just teach people to debate the loudest or the best about their position. Ethics is often thinking about sort of a creative third option, and that often requires getting a lot of people with a lot of different expertise in the same room who can think creatively.

So on this slide, I'm just putting out two different options for adaptive approaches as it turns out that the second one is essentially what the NIH trial is doing. I'm putting them both out there partly as examples and partly just to continue this thinking that let's think outside the box a little bit and we don't only have to debate placebo versus non-placebo, 50/50 randomization versus everybody gets it.

So Adaptive Approach 1 is to some degree in my mind responsive to people who say you may be denying sick people a lifesaving treatment. And again, everybody watched -- a lot of people watched Kent Brantly walk out of that ambulance, and boy, did that change people's understanding or belief about what they thought ZMapp could accomplish.

So one way to respond to that narrative would be to do an adaptive trial where you collect -- you maybe call it a pilot study, but you give everybody, a small number of people who are sick, the experimental treatment. And you will see even without a placebo an effect only of a magic bullet dramatic drug, what I think Lu called a super -- home run, home run.

So if out of 40 sick patients, 38 get up a week later and walk away, you don't need a placebo. I'm not sure that anybody is expecting that, but the truth is, you would learn that. You would also learn fairly quickly and I think potentially send a message to people who are feeling desperate and anxious, understandably, if 38 people didn't walk out and you're actually not really sure based on the numbers because the historical data aren't reliable, whether the drug made a difference, you actually have a lot more ethical justification for introducing a placebo. It may be that the drug is helpful, but it may -- it's probably true that it's not as dramatically lifesaving. So if it's unclear, you need to use a placebo but less troubling.

Another approach is an adaptive approach where people are randomized to a few different treatments as part of the randomization. Supportive care may be even more important here.

And I guess my last message which builds a little bit on what Clement said is I understand that these are our key questions, but it's also really important when we think about the U.S. response to think about what else makes a difference.

Our goal is to, as Dr. Gutmann was saying at the beginning, really think about preventing the spread of really bad epidemics soon after they hit. And vaccines and treatments only get us so far. Public health response is going to be the biggest intervention, particularly in new epidemics. And a lot of research on messaging, on what approaches are the most accessible and make the most sense to people, what messages are the most accessible probably will be the most successful.

So I'll stop there. Thank you.

DR. GUTMANN: Thank you all very much. Terrific panel. I'll kick off the questioning and then open it up for other people to question.

We're using the example of Ebola for two reasons. One, it's incredibly important in its public health consequences and its sheer effects on people, and that would be a sufficient reason. But secondly, it is a great, an important example for public health more generally and public health emergencies for contagious diseases.

So you have rightly honed in on one very important place, which is what we like to hone in on, where ethics and practical effects intersect, and that is randomized controlled trials. Is that the right way forward?

And I heard at least two of the three people say that's the right way forward, although Luke -- do you go by Luke? Lu. Okay.

So I'm going to call you each by your first names and you may call me in return.

So Lu said adaptive randomized controlled trial is the way to go. Nancy proposed an alternative to begin with to see if there's a home run.

Clement, I'd like you to say what you think on this issue and why.

DR. ADEBAMOWO: Thank you very much.

So our position is that indeed, randomized controlled clinical trials provide the highest level of evidence, but in the context of the public health emergency that we're facing, we were happy to allow adaptive drug use exactly like the first example that Nancy made in which affected individuals are exposed to putative efficacious therapies and data collected and analyzed.

DR. GUTMANN: And if it's a home run, then you use it, but if not, you go on to a controlled trial, as Lu suggested?

DR. ADEBAMOWO: Yes.

DR. GUTMANN: I'm going to stop there because I --

DR. WAGNER: You can't stop there. You got to ask Lu.

DR. GUTMANN: Oh, yes. Right, so I won't stop there. You're absolutely right.

What about Nancy's --

DR. BORIO: So I think it goes back to the idea of the home run, right, and then in the absence of a product that is predicted to have a home run, I think that the way I think about is how many lives -- in the background of the epidemic, we have daily deaths, and how many in that delay for doing two trials instead of one, how many more lives could have been saved by going straight ahead to an adaptive randomized controlled trial. So that's a tradeoff there.

DR. GUTMANN: So let me just say we came late, we the United States came late to doing a controlled trial on this, right? And one of the -- that is, there were

people calling for research trials. I understand resources are constrained and so on, but we are just now doing them. And what your position is -- and I'm not pointing fingers at anyone. I'm just saying your position is it's time to get on with a randomized controlled trial. We have no time to lose.

DR. BORIO: Yes, so some clarification, I don't know that we could have gone any earlier because the products that the U.S. government has been developing, for example, ZMapp, is just now this week coming out of lot release and becoming available for study in trial. So that's --

DR. GUTMANN: So let me -- that's why I said -- I'm not saying the government could have now gone earlier. There were researchers calling for research that would have positioned us to have the information that we now have earlier. But given what information we have, we can go now.

DR. BORIO: Given the products we have, we can --

DR. GUTMANN: Given the products we have, yes. So your position is we should lose no time in doing a randomized controlled trial?

DR. BORIO: That is my position.

DR. GUTMANN: That's what I heard. I thought it was as clear as -- Nelson.

DR. MICHAEL: Again, thanks for allowing us to use first names because I've never called Lu anything other than Lu.

So my question to you, Lu, is you spent most of your remarks talking about the really important reasons for why efficiently -- I think that's the term I first heard you use in Geneva -- why efficiently one wants to get to an answer to best help individuals, and the way to do that, if possible, is through a randomized controlled trial.

So a lot of your remarks were focused on therapeutics, and I'd like to hear your guidance on how we can inform the debate to not conflate between therapeutics and vaccine trials because I think that a lot of the more emotional issues, if I can use that term, that surround therapeutics, people are dying, we need to do something right now, anything works, these three guys survived, who knows what they got, but they walked out of an ambulance to then segueing to vaccines where individuals are at some degree of risk for developing acquisition of Ebola virus infection and some of that risk may be zero. Yet you're exposing them to experimental vaccines.

And we in the HIV field have a singular example of a vaccine that actually caused people to become more likely to become infected.

So how do we inform that debate to sort of keep those two camps,

preventative vaccine approach and therapeutics from a bioethics standpoint in different bins?

DR. GUTMANN: Anyone can answer -- Lu, you take, but I am happy if you want to answer any of these questions. We don't have to have everyone answering all of them, but if you want to, just tell me.

Lu.

DR. BORIO: I'm not sure that I completely understand the question, so.

DR. MICHAEL: The ethics of considering randomized controlled trials for vaccines versus therapeutics. In therapeutics, you are inherently taking somebody who already has disease. They are in a different risk category. It's a different ethical debate than in someone that is not currently infected but might be at some level of risk, and yet you want to give that person an experimental vaccine.

So the use of placebos in those two situations, in my view, is ethically very different, night and day different. So I just wanted to get your opinion on that.

You spent most of your remarks talking about the use of placebos in the context of therapeutic studies, not vaccine studies.

DR. BORIO: I don't think it's -- it may be different conceptually. From a practical perspective, I think it's pretty much similar is that we don't know whether these products work. We really do not know, and for us to be able to benefit populations in the future, we need to know whether these products work.

And the most efficient way to do that and most definitive way to do that is to do the trials that NIH and Liberian authorities launched in Liberia this week.

DR. GUTMANN: Nancy.

DR. KASS: I share your concern deeply, and obviously, a placebo controlled trial is the most efficient, but how comfortable we feel ethically sort of allowing these trials to go forward not only in general generically with a vaccine trial where you're giving something where we don't have a lot of safety information yet to people who are healthy. And that's very different than giving something to somebody who's sick.

But particularly as the incidence falls, and I should have -- I'll say as a piece of disclosure, although nothing in my remarks was relevant to that, that I've been asked to serve on the DSMB for the NIH vaccine trial. And I don't look forward to engaging in these discussions that, of course, we're going to have to have about how much -- what kinds and how much safety data concern will be enough to say the trial should go forward or shouldn't forward, particularly because if epidemiology continues

the way it has been, there's going to be another Ebola outbreak at some point.

So we're going to want to know if this vaccine is effective, but for the 27,000 people enrolled, it's not the same equation as we even thought it would have been three months ago.

DR. BORIO: I'll add a little bit to that then. So I think this -- I begin to understand the point now, and I think that the way -- so clearly, we want to be able to conduct studies that will yield actionable information to us. And I think that that's exactly what the researchers are doing right now is we have to make sure that the designs -- that the study is implemented in a way that allows us to follow the safety signals very closely, that allows us to adapt a design, that allows us to make modifications.

We have to be very aware that the studies -- again, these are highly accelerated programs and that we need to be able to be ready to be flexible and make changes as we accrue new information. And as an example, the fact that it's -- the sample size may need to change. Some of the -- we're looking into adding a lot more immunogenicity data collection into the studies because we think that that would be very critical information to have in the event the clinical endpoint cannot be achieved.

So the bottom line is that we need to adapt. It's all adaptive.

DR. GUTMANN: I have Dan next. I have Christine down too.

DR. SULMASY: I heard Clement beginning by talking about the 1996 epidemic and the way that it informs the Nigerian statement now, but I didn't hear anything in the rest of the remarks that connected the two. So I'd like to hear a little bit more from you about what happened in there, what the lessons were that you think are important for thinking about trials now.

DR. ADEBAMOWO: Thank you very much.

So the 1996 epidemic largely taught us, number one, that the time to think about what to do in the middle of an epidemic is not when one is occurring. And so what we did was the lessons we learned, we incorporated them into the national guidelines for research ethics in the country.

So we didn't really have to issue any specific statements or guidance related to what we needed to do with the Ebola virus disease epidemic, but we were able to go within the guidelines that were already in place. And every ethics committee in Nigeria was supposed to or was complying with and used those principles to guide our response.

I think the important one element that we really -- that I tried to convey, maybe I didn't do a good job, is the fact that there is a certain circular trend to the

disease epidemic which influenced our opinion and ought to influence our response to it.

So there is no randomized clinical trial that has shown that best supportive care is the best treatment for people with Ebola, and there has been a whole host of new drugs that have developed first by people using them in a non-randomized clinical trial setting, obtaining data which then they took forward into randomized clinical trials.

There were also concerns with many of my colleagues and in the discussions that we had that if some of these therapies were being developed in the affected African countries, they would have used them and quickly, too. And what if that did not work? We won't know. So it was now likely to be the case that people are going to be exposed to treatments that were more than likely to harm them than, well, the best supportive care that they were getting.

Indeed, in the Nigerian experience, a lot of "potential therapeutic agents" were presented to the ethics committee, and they were never approved to be used on patients with Ebola because we've said look, all the precedent data just does not fit. It's not like this is an agent that has been approved for other viral illnesses and reasons to believe that the pathways are similar, et cetera. So I just thought I should mention that.

DR. SULMASY: To follow up, so I'm clear and I understand, in some ways, you would think of using a particular epidemic as a setting in which to do the equivalent of Phase 1 trials that would be useful to do in a randomized trial when the second epidemic comes. Is that the way you're thinking?

DR. ADEBAMOWO: Basically, because at least as far as I know right now, we don't know endemic forms of Ebola. Every time it has occurred, it has been an epidemic. So there is no other natural experiment or natural environment in which to study these interventions, as far as I know.

DR. GUTMANN: Christine.

DR. GRADY: Thank you each very much for your presentations and interesting discussion.

I want to make two points first because I think they're so important that I don't want us to lose them, and then I have at least one, probably three, questions.

The two points -- I'll stick with one because I know the rules. The two points that I want to make is I think many of you said that the most critical thing is that when we do research in any way if we can't answer the question, it's not an ethical endeavor. And so I don't want us to lose that because I think that's really important.

The other thing that I think is really important and I agree with the way Nancy presented it and Nelson asked it, I think that there are significant ethical

differences between treatment trials and vaccine trials and that they need to be thought of differently.

The question I have actually is about best supportive care. So I think one of the dilemmas in setting up a trial with any design actually is that there are questions about best supportive care, that there are variations in best supportive care, that there are at least some people who believe that certain kinds of best supportive care change the mortality rate and the whole outcome significantly.

And I hadn't thought about this so much before until Nancy brought it up, but I think a similar question actually underlies the vaccine trial in terms of what other things do you provide in the setting of a vaccine trial. It's sort of the same question. If you provide lots of protection and you provide lots of things that reduce the incidence of the infection in other ways, you're changing the background.

So that's the question, and I want to frame it one more way. And that is, I really appreciate what Clement said about sort of the background conditions in terms of what people trust, how they understand research, what the kind of infrastructures and economic situations that they are currently living in, how that matters, too.

And so I want to ask the question what do you think -- how do you think we should think about best supportive care when we're designing a randomized trial? Should it be done in the places where these treatments will ultimately be the most sought after, or should it be done in a place where we can control the best supportive care in a way that gives us a better answer?

DR. GUTMANN: Clement, do you want to take a shot at that because it really is something you've had a lot of experience and thought a lot about, which is if you're doing a trial, do you do it where you can give the best supportive care and control best for that, or do you do it where it's most likely to be used?

DR. ADEBAMOWO: We engage with this problem and extended the discussions considerably. For example, what precisely constitutes best supportive care? I mean, do you have to have renal dialysis, for example? Are you going to be able to support ventilation in cases of respiratory failure? And these are resources that are extremely scarce in the infected environments.

So our response was to say if you're going to enroll people in a clinical trial of -- a randomized clinical trial in which the non-intervention arm is best supportive care, then it has to be best supportive care in the places where you're going to be using the intervention because that to us appears to be the most appropriate comparator in this situation.

DR. BORIO: Perhaps may I add a few things?

DR. GUTMANN: You may. Go ahead.

DR. BORIO: So I completely agree, and I think the trial is fairly flexible and agnostic in that way. One thing we have to keep in mind is that a product may actually have a greater benefit in a setting of less supportive care. Alternatively, a product may require a certain amount of supportive care to be able to show benefit.

And I think that again the studies that -- the protocol that NIH developed can be implemented in different settings. We do have to keep in mind that some products --

DR. GUTMANN: So, Lu, can I just interrupt you for a second? So it's fair to say that what we need to begin with in line -- we have a principle that you have to do the best science to do the best ethics. So you have to do your best determination of what -- how this product is most likely to be beneficial.

And it's a guess, but then you -- so it's based on what you know to date.

DR. BORIO: And we never envisioned -- and we wouldn't envision a trial where a requirement for the trial would be to have dialysis and ventilation support in an west African setting because that's not realistic. It needs to be benefit although we --

DR. GUTMANN: So that underlines what Clement is saying.

DR. BORIO: Yes, although we all recognize also that improving the medical delivery framework would go a long way generally for the broader public health in the area.

And also, but we do have to keep in mind that some of the products, though, would not be appropriate in an unmonitored setting. We have products that would cause hypertension, cytokine release and those products frankly would not be appropriate in an unmonitored very rudimentary setting. And we should take into consideration whether those products would be studied in the most bare of settings.

DR. GUTMANN: Good. Thank you.

Anita, did you want to follow up on this, or is it a different question?

DR. ALLEN: I think --

DR. GUTMANN: Okay. So let me go to John and then Anita.

DR. ARRAS: Thanks for a great panel.

I want to connect up Nancy's first slide with the rest of the discussion. In other words, what is the relationship between public health ethics and research design? And with the proviso that we're not simply talking about garden variety public health ethics here. We're talking about public health in the context of a catastrophic epidemic,

right, where almost by definition the medical infrastructure is overrun.

So we've heard from Lu that the way to respond to this situation is to go from a standard brand, gold standard RCT to an adaptive RCT. So I'm wondering what is the motivation for going to an adaptive model instead of the standard RCT model. Is that because of the catastrophic nature of the setting, or is it just the best way of doing research, in which case we should make the adaptive RCT the new gold standard?

DR. BORIO: I don't think I'm qualified to answer that question. Everything I've learned about adaptive RCTs I learned from NIH and FDA statisticians, but I think there's a general trend in increasing use of adaptive RCTs.

As we learn more about clinical trial designs and the science of clinical trial designs, they do have quite a bit of -- some important characteristics that are fairly attractive for product development in general.

DR. ARRAS: Could you just -- I know we're all just groping here, okay? But could you elaborate a little bit on that for me. Like, what, in fact, are the big differences between a standard brand RCT and an adaptive version because I just -- in the literature that I see, I just see a lot of hand waving.

A lot of it's very vague, so what, in fact, are the advantages, concrete advantages of going to an adaptive design?

DR. GUTMANN: Since we have members of the commission -- I'm going to ask Nelson to answer actually because he put his hand up to answer this, and I think we need to answer it because I don't think it's hand waving.

DR. MICHAEL: This will prove to you that Lu and I are battle buddies, okay, because we've dealt on the vaccine side with adaptive design in HIV a lot.

And the bottom line is, you saw the design. You basically sort out the dogs. The point is -- let's say you have four vaccines that are all ready to go all at the same time and four different manufacturers are all completely jiggy with you doing the cookoff.

Now, what's the chance that's going to happen? Zero, but theoretically that could happen, so you have four vaccines. They all go at the same time in a high risk zone. Fill in the disease you want. It could be HIV. It could be malaria. It could be Ebola virus. And you have a single common placebo arm.

So this gets back to Lu's point about it being extremely efficient. Now again, that sounds great to the DMSB. Now we know that Nancy is one of those kinds of people. She sits there and stares at all the incidence data, and the thing you want to initially -- even very early on if you have enough incidence, enough attack rate, you see that one of those arms is accumulating lots of disease whereas three of the four other

arms kind of are tracking the same, but they all look better.

So guess what? The DMSB says stop arm number 4, re-randomize those people into other arms and go.

Now, this is, as Lu mentioned, is much more common to be seen in the oncology world and in drug development because drugs are more likely to be able to start the race at the same time. For vaccines, it's extremely difficult.

And this is really an exemplar of this approach for vaccine development that NIH is taking in Liberia.

DR. WAGNER: I just want a clarification because the suggestion is that the -- now that there is no advantage to the science, remember the premise we're working on is Christine's premise, what she said. There is no ethical science if it doesn't answer the question.

And if what you're saying is adaptive methods always answer the question, they're always ethical, I think it's an important point. Would we be recommending it universally, or is it really recommended because there really isn't a separation between Slide 1 and Slide 2 [in Dr. Kass' presentation] that's absolutely a bright line, that there is an element of compassionate response. And we imagine that there is slightly compromised the -- you see what I'm saying?

That we are happy to slightly compromise the ability to have the best data that a true gold standard RCT would do, we're comfortable with compromising that with adaptive RCT. And if it's not a compromise, then to your point.

DR. GUTMANN: So I'm going to give my answer, and then you can agree or disagree with it. I believe the way it's presented, the way that Nelson and Lu presented and at the best practice, adaptive RCTs are the best practice.

DR. WAGNER: Period?

DR. GUTMANN: Period.

DR. WAGNER: Regardless of setting?

DR. GUTMANN: Yes, because it's always better to know sooner whether there is a better way of treating people, and if that -- and that's what public health emergencies do is they make it all -- they focus us all the more keenly on doing it in a time efficient way to save lives. And it's always better to save more lives.

Now, to the extent that it compromises by the scientific findings, there's a tension in the public health side, emergency side, and there's a tension regularly. And there you just have to go with the best judgment you have as to whether it's time to stop

the trial and give the treatment, and that's no different in emergencies than in other cases except that the emergencies highlight the lives that could be gained or lost here.

DR. ARRAS: Can I follow up just quick, and this is a question for the panel.

DR. GUTMANN: But wait, wait. I'm going just keep an order. Christine is supposed to follow up –

DR. ARRAS: Sure, sure.

DR. GUTMANN: -- and then we'll get back to you, John.

DR. ARRAS: Okay.

DR. GRADY: Well, I just want to say something on this topic of adaptation because I think -- I don't think we should say universally RCTs or universally RCT and adaptive trials is the right way to go. I like the way that Clement started out –

DR. GUTMANN: We're not saying that.

DR. GRADY: -- that there are several things that need to be taken into account in every case, the biology of the disease, the drugs in the pipeline, the facts on the ground, et cetera.

And there are multiple different types of adaptation, and we need to -- they need to be evaluated on all of these terms.

DR. GUTMANN: So it's my job just to keep us what we've said. So any -- John's question was are we saying that adaptive RCTs are -- this was Jim's -- are always better than RCTs. And the answer there is yes. I mean, it's always best to begin with the adaptive RCT model because -- for reasons we gave.

Then the question is, is it always best to have a randomized clinical trial, and Christine's view is no. I mean, there isn't -- you don't always begin with a randomized clinical trial.

Is that what you were saying?

DR. GRADY: You don't begin with a randomized clinical trial without thinking about all the important details of why that's the best design or if it isn't the best design.

DR. GUTMANN: Which means you don't always begin with it –

DR. GRADY: Right.

DR. GUTMANN: -- because otherwise, you wouldn't have to ask the question. I'm just -- not --

DR. GRADY: Right, but I think it's an important point because some of the somewhat acrimonious debate out there has been between different types of trials, and some of them are adaptive trials.

DR. GUTMANN: We get it.

DR. GRADY: And some work; some don't. It depends on the details of why you're doing it that way and what the adaptation is.

DR. GUTMANN: Agreed. I'm not trying to get rid of the reasons. I'm trying to see where we're establishing agreement here for the reasons that have been given.

John.

DR. ARRAS: Yes, so --

DR. GUTMANN: And, Anita, I haven't lost track that you're -- and I have one question that I'm going to do.

DR. ARRAS: Just to pursue this point a little bit further, okay, and for the sake of argument, I want to channel Bob Temple here. So he's a defender of the standard randomized clinical trial. I think somebody like Temple might say, well, adaptive trials may give up too quickly. They may see a trend emerging, but for all we know, if we waited four more months or five more months, things would even out and we'd get a different result.

So I'm just wondering if there is really a cost in terms of rigor to using adaptive trials. Is there a possibility that by just eyeballing it early on in the study that you could foreclose the possibility that a slow starting treatment could eventually come through later in the trial if you just gave it more of a chance.

DR. BORIO: So Bob has been working very closely with us in these issues. And I think that goes back to Christine's comment that there are many different types of adaptation.

So the adaptive randomized controlled trials that we developed for this particular situation, knowing about this disease and the drugs we have available, is a design where we believe is superior to the 50/50 sample size fixed, randomized controlled trial.

And Bob, let me channel him, he's fine with that.

DR. GUTMANN: And look, you can do adaptive -- put the word "adaptive" or any other word before randomized, you can do it well, and you can do it badly.

Anita.

DR. ALLEN: Thank you.

I just want to say that this panel has been just a model of clarity and helpfulness. I just think it's been terrific.

I have two short questions, and the first one is for Nancy. You referenced the duty of reciprocity, and I was really interested in that in the context of vaccine trials and who we might use as our target population for such a trial. And you mentioned healthcare workers and family members.

I just wanted you to say a little bit more about your understanding of this duty of reciprocity because who do we target, who is the who who decides who we target and who do we target and what are the reasons that we think we owe them something and are there expectations that we owe them something?

I mean, the healthcare workers, I understood your point. I know that some nurses are up in arms about the lack of care for them in the context of their clinical work and they also think that there that reciprocity is a reason why they should be having better equipment and so forth.

But in the vaccine context, just say more about why you think that healthcare workers and/or household members would be owed this duty of reciprocity, sort of what is it.

And in connection with that, I just wanted to ask Clement whether in the African context -- in the Nigerian context, that same concept of a duty of reciprocity would resonate with healthcare workers and/or household members and whether they would have an expectation they would be privileged or picked out, targeted for early vaccine trials.

DR. KASS: Great. Thanks, Anita.

So do we owe something to the healthcare workers to me is an unequivocal yes. So whether we owe something, I'll start by saying in general, to healthcare workers who are willing to step forward and work in this context, an extraordinary yes. And there are things like personal protective equipment, and there are things like doing our best to get them as good care as possible as soon as possible if they become sick.

So that to me is a separate question from whether they ought to be the target population for a vaccine study, and I think it's very easy to conflate them. In my view, I think it makes sense to target where you're going to have again the most efficient population. It's very complicated ethically because what you're saying is you want to go to the people where there's the highest incidence.

It's the reason why in a lot of HIV trials, they've been targeted toward injection drug users and commercial sex workers which has its own array of ethical issues. I don't need to convince this crowd.

And yet, it makes a lot of sense to do that. So I guess I'll just say I think it does make sense to go with efficiency.

The complicated thing, in my view, is what then happens if it turns out that you have a beneficial product. Maybe the world will be great and you can roll it out to all the populations fast and you don't have to make tough choices. And if you have enough product, that's great.

But I think it gets to be really hard if you then have a limited number of vaccines, and you owe something to these healthcare workers but it's the household members who participated.

DR. ALLEN: I'm just a little puzzled, though, about –

DR. GUTMANN: I'm going to –

DR. ALLEN: I know we're short in time, yes. Okay.

DR. GUTMANN: I really need you to let Clement answer because we're going to go over a little, but we can only go over a little.

DR. ADEBAMOWO: Thank you very much.

So indeed what Nancy said did reciprocate, but I'd like to channel some of the other arguments that we heard when we were discussing this in Nigeria.

And some of that included healthcare workers already have all these sort of protections, and so maybe those community members who don't have all these moon suits, as they were called in Nigeria, should be the ones to have priority in getting the vaccine.

Maybe healthcare workers do not represent the generality of the population. Maybe they are richer. Maybe they have better nutrition and better immunological profile, and therefore, we really will not be getting a real-life experience of the vaccine.

And all of these things were put on the table, but we did agree that in the context where, in fact, with the Ebola virus, this epidemic, the single most affected occupational group were healthcare workers, and many were not going to work out of fear and because they felt that the system may not take care of them if they were to fall ill.

In that kind of context, I think one cannot find fault with Nancy's arguments.

DR. GUTMANN: Steve, you had a question, and I have a question from a member of our audience.

DR. HAUSER: So I was going in a different direction.

DR. GUTMANN: That's okay.

DR. HAUSER: And I can defer until later.

DR. GUTMANN: No, you can ask your question.

DR. HAUSER: So is it all right if we shift?

DR. GUTMANN: Yes.

DR. HAUSER: Just I might say one thing that I think has been emphasized by a number of the commissioners which is it sounds as if there's consensus on the importance of flexibility, given the fact that there's clinical equipoise, that's why we're doing trials. And balancing the judgment of experts that will not always be the same about effect size, the likelihood in multi-arm studies of similar effect sizes in one or the other, the influence that that has on the number of people enrolled in the trial and this concept that you go back to which is so important about efficiency and speed.

So we are dealing with unknowns, and I think to be very prescriptive about details would be -- might not be helpful.

The question that I wanted to ask has to do with the problem of compassionate use once an RCT has begun and how we go forward with that in a just way, especially for something like ZMapp where quantity may be an issue.

DR. BORIO: Yes, so we have a long tradition where once an RCT is established, compassionate use of a product must not interfere with the conduct of the clinical trial. So, for example, in the U.S., once the RCT is established, ZMapp would be available through enrollment in the clinical trial. Again, because of the greatest good for the population is for us to establish definitively whether the product is safe and effective.

DR. GUTMANN: Can I just -- since I could see your -- as you were saying it, you were thinking perhaps what I was thinking. So in the clinical trial, ZMapp has to be used the way it's necessary for the control, but ZMapp is prescribed for lots of -- outside of -- what about outside of the clinical trial, would there be compassionate use of ZMapp even before the results of the clinical trial?

DR. BORIO: Well, for example, in ZMapp, given limited supplies, product would be available only for patients enrolled in a clinical trial.

DR. GUTMANN: So it would be prohibited? Doctors would be prohibited from using it.

DR. BORIO: They may request, but for the compassionate use of a product really that is determined by a physician asking the company making the product available on a risk-benefit evaluation on a case-by-case basis. Given the supply, it'd be very unlikely for the company to make that available outside of the clinical trial.

DR. GUTMANN: Okay. I want to read a question from Dr. Seema Yasmin who will be presenting tomorrow -- this afternoon actually.

And, Dr. Yasmin, where are you? Welcome.

She's a professor of public health at the University of Texas at Dallas and also a journalist with the Dallas Morning News.

Her question is the following: The rate of new infections is the lowest it's been since last June, about 100 cases per week. This makes it very challenging to conduct trials with sufficient power. How does this factor in to our discussion of the most efficient and ethical study design?

Lu, do you want to take this?

DR. BORIO: Sure. So this is the question that journalists have been asking me all the week, and first, we don't know for sure what the trajectory will be. We hope that this is towards the end, and second, we think that with the ongoing number of cases, we still could come to a very definitive answer.

The trial again is quite efficient, and depending on the magnitude of the benefit of the product, one could reach conclusions with relatively few number of patients and certainly within what's happening today with the epidemic.

And lastly, I have to -- I'll say that even if -- the alternative, not beginning a trial, we will learn less than if we start the trial. Even if the trial cannot come to completion for reasons where -- the epidemic could just melt away in the next week, dosing patients in the setting of a trial will still let us accrue significant amount of knowledge as compared to dosing patients outside of a trial.

And it certainly -- if you think about the alternative which is the animal rule, those studies are relatively small and in non-human primates generally. So again, think about the strength of the data that we can accrue from animal rule versus using the product in the clinical setting.

DR. GUTMANN: Could I flip this and ask you, would you say that it is urgent that we do this? A hundred cases a week, with all due respect to our presenter this afternoon, is a lot of cases of a deadly disease that we're getting a week. And it would seem from what you've said that it's actually urgent that we conduct this so we find out something in a controlled scientific way where we now have almost no --

DR. BORIO: It is urgent, and we can do this if we work together and if -- with the support of the affected countries, we can still do this.

DR. GUTMANN: Clement, would you weigh in on this?

DR. ADEBAMOWO: I guess these are some of the concerns that people have, that this epidemic is going to burn out before the machinery of randomized clinical trials does -- get into gear. I guess we're going to find out soon.

DR. GUTMANN: But you would say that that means we have to do it as soon as we can because time is of the essence.

DR. ADEBAMOWO: Yes, as soon as we can. Yes.

DR. GUTMANN: Nancy, do you want to say some conclusions on this or any other question that you feel you haven't -- you want to answer more? You don't have to.

DR. KASS: I think the only comment I'll make was on the previous discussion which is to underscore, if I could sort of -- I felt like I could hear a recommendation coming -- to maybe use language that is more than adaptive trial if you make a recommendation for that because there are lots of designs that count as adaptive.

And my guess is from listening to your conversation, there are some you would support and some you wouldn't support. So I just would be really careful with using that language exclusively without further explanation.

DR. GUTMANN: Well, we always give explanations --

DR. KASS: I know you do. I don't mean that to come across without humility. I apologize.

DR. GUTMANN: No, it's a comment well taken, but I'm going to ask you to do something post this which is give us what you think are the distinguishing factors between those adaptive random clinical trials that are scientifically sound and in this

context, urgent, and those we should be wary of.

DR. KASS: Great.

DR. GUTMANN: Okay?

And on that note, I think you all could tell how incredibly useful your comments were and spot on directive to our charge as -- our self-charge, I should say, as a bioethics commission.

So with that, I'd like on behalf of all of us to thank you.

(Applause.)