



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

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Amy Gutmann: Good morning, everybody. I'm Amy Gutmann. I'm Chair of the Presidential Commission for the Study of Bioethical Issues, and it's my pleasure along with our Vice Chair, Jim Wagner, who is President of Emory University and my partner with our colleagues here. It's my pleasure to invite you to the seventh meeting of the commission's deliberations. This is day one of our seventh meeting.

I also want to thank our wonderful member of our commission, Dr. Kucherlapati who is a member of the Harvard Medical School faculty, for hosting us here and for the whole—to the whole Harvard Medical School administration for having us here. I want to recognize our executive director, Valerie Bonham, who is our designated federal official. Val, would you please stand up so people can see you?

At this meeting, we are going to focus solely on a very important charge from President Obama that is a charge to respond to the subject of the protection of human subjects participating in research supported by the federal government. The president asked us to conduct a thorough review of contemporary subjects protection standards. The president further asked the commission to assure him that current rules for research participants protect people from harm or unethical treatment, both domestically and internationally.

We take this assignment very seriously. It was prompted by the revelation that the United States had funded STD research in Guatemala in the late 1940s that involved intentional exposure of vulnerable populations including prisoners, mental patients, and children to STDs without their consent. The president asked us to conduct both an historical investigation into what happened in Guatemala and also a contemporary assessment of the rules and regulations governing human subjects research today, and I would add not only the rules and regulations, but the practices that actually happen on the ground today.

We released our historical investigation in September, and the contemporary report will be completed next month. The commission has overseen a number of efforts to help us respond to this contemporary charge. I have spoken before about the international research panel convened as a subcommittee to this commission. We had, on that panel, very eminent international experts in both medical and human subjects research and bioethics including a group of members of this commission who also served on the panel.

The panel reported its findings and recommendations to the full commission in the form of a report which we entitled, "Research Across Borders." That report was released on our website and also in print, and we published notice of the report in the federal register and we took public comment on it for 30 days, all of which was enormously helpful to us.

We also conducted an extensive empirical project, and that collected data from government agencies that support research involving human subjects. We asked agencies that follow the common rule for human subjects protection to give us basic information about the research they support including the study title, the principal investigator, funding location, and number of participants. With this information, we are able to describe to the president the landscape of human subject research supported by the federal government domestically and internationally, and we will discuss the empirical project further today in session two and indicate where it shows strengths and where it shows challenges remaining in that area.

As many of you know, our work on human subjects protection dovetails very nicely with the reform work that's already underway by the US government. The advance notice of proposed rulemaking ANPRM, which I've learned to just roll off my tongue, which was released last summer reflects many of the concerns we have heard in our prior meetings and the public comments submitted to us about current human subjects protections and the system that governs it. We have

put a lot of thought into the proposals in the ANPRM, and we will address many of them today and in our forthcoming report.

Finally, as a preview of coming attractions, I just want to mention that we're also moving ahead on our next project called, "Genes to Genomes, Collecting, Using, and Governing Genome Sequence Data." That project will address how the growing amount of collected and available genetic data raises the bar on data protection, privacy, consent, and counseling among other issues, and we will devote the spring and summer to this subject and produce a report after that. We will also begin diving into another important topic tentatively called, "Neuroimaging and the Self," which will focus on advances in neuroimaging and the implications for moral and legal responsibility.

So before we begin, I would like to say a few words about how we will take comments from the audience in this meeting. It's worked very well for us in the past, and we hope that members of the audience will participate. At the registration table out front, there are comment cards. We ask that you write down any comments you have on these cards and hand the card to any staff member. They're all wearing name badges, and will staff members stand up, please, so everyone can—there they are. Hand them to anybody, and the staff will give me the cards throughout the sessions, and time permitting, Jim or I will read them aloud and have a response from some member of the commission or a presenter. We just ask that you make the questions relevant to the session in which we are in.

I'd like to ask Jim Wagner to say a few words, and then I'd like to ask the members of the commission to introduce themselves. So, Jim—

James Wagner: Sure, sure, just to add a very few words. As usual Amy, you covered most all of the bases. Let me add my welcome to all the commissioners. Welcome to our guests. Welcome to those in the hall. Special thanks to the commissioners for all the work you've been doing in small groups off line, just an intense effort to move us toward this meeting where we can exchange meaningfully.

The impetus, and perhaps I don't need to—certainly, I don't need to tell the commissioners this, but more broadly, reminding everyone the impetus for what we are doing has been the charge by President Obama which is one articulation it seems to me of an even larger goal to help ensure that the way we undertake human subjects research protects, encourages, and makes fruitful what is really a selfless practice of research subjects to accept medical treatments and therapies that are really intended most often not for their benefit, but for the benefit of others. So through the work we're doing, we hope to encourage a clarity and practice of ethics that complemented by a necessary and presuming minimum necessary set of regulations to ensure that subjects of research are protected and that investigators are motivated not just in response to the pressures of oversight, but rather more by genuine concerns for safety, well-being, and dignity of those of those who volunteer as human subjects so that regulation is understood to facilitate ethical practice rather than understood as a substitute for it.

So I look forward to the exchanges we're going to have here, and I look forward to the wisdom and experience that our guests will bring us. With that, I'll turn it back to our chair for introductions and to start our initial session.

Amy Gutmann: Yeah, I'd like to ask Nita to begin and just have the members of the commission introduce themselves.

Nita Farahany: Good morning. I'm Nita Farahany. I'm an associate professor of law and philosophy at Vanderbilt University.

Dan Sulmasy: Dan Sulmasy, the Divinity School and Medical School of the University of Chicago.

Christine Grady: Christine Grady of the Department of Bioethics at BNHI Clinical Center.

John Arras: I'm John Arras. I teach philosophy and bioethics at the University of Virginia.

Barbara Atkinson: Barbara Atkinson, I'm from the University of Kansas Medical Center, the Executive Vice Chancellor and Dean.

Anita Allen: I'm Anita Allen, professor of law and professor of philosophy at the University of Pennsylvania where I'm also a fellow in the bioethics center.

Raju Kucherlapati: Hi, I'm Raju Kucherlapati from Harvard Medical School.

Lonnie Ali: Hi, I'm Lonnie Ali.

Stephen Hauser: Hi, Stephen Hauser from the Department of Neurology at UC San Francisco.

Nelson Michael: I'm Nelson Michael. I'm an AIDS researcher at the Walter Reed Army Institute of Research.

Amy Gutmann: I would just like to also thank the members of this commission for really hard and good work. We've all, as I've been reminded multiple times just daily, everybody here has day jobs, and they've also been working night shifts, late night shifts, on really moving this very important project forward.

The federal government as well as private industry are bound to abide my many standards fundamental to the protection of human subjects in research including, for example, the independent review of studies and obtaining informed consent. In this session, what we'd like to focus on is probing whether these standards are perceived as obstacles to the researchers or as essential to what good science and what their ethical and professional standards inform them to do. In other words, is it seen as integral to the profession to have high ethical standards of the sort that we are, as a commission, charged to assure the president that they are actually abided by.

So, to begin our discussion, I'd like to welcome our two speakers in this session, Dr. Russell Medford and Mr. Jeffrey Francer. We're very eager to hear your thoughts on this, and we know that you have a lot to tell us. We're interested to hear about the standards your organizations promulgate for clinical research and some of which may go beyond what is generally required for federally sponsored research, and we'd also be interested to hear what you see as the actual practices based on those standards.

So, let me first introduce Russell Medford who is the chairman and president of Salutria Pharmaceuticals. Dr. Medford also serves on the Biotechnology Industry Organization's, BIO, Board of Directors and the BIO Emerging Companies Section Governing Body. He is co-chair of the BIO Board's Standing Committee on Bioethics. From 1995 to 2009, Dr. Medford served as President, Chief Executive Officer, and Director of AtheroGenics, Inc., a public health

pharmaceutical company. Welcome, Dr. Medford. We look forward to your comments.

Russell Medford: Thank you, Madame Chairwoman, members of the commission, and the staff, for inviting us here. I'm Russell Medford. I'm the CEO and President of Salutria Pharmaceuticals and importantly, I think for this discussion, someone who's had extensive experience, both from the academic side as well as the industry side in the conduct of high quality and highly ethical clinical trials to address major health problems in the areas of cardiovascular disease and diabetes.

BIO itself is a trade organization based in Washington D.C. that represents over 1,100 life science companies around the world, and our members are performing important research to develop treatments and cures for a variety of diseases such as diabetes, heart disease, and cancer. This research has already led to the development of over 250 drugs and biologics with hundreds more in clinical testing.

As my colleague, Mr. Francer, will say in his remarks as well, the industry, both the pharmaceutical and the biotechnology industry, conducts the vast majority of clinical trials, both domestically and internationally. We have a wealth of experience in addressing the very issues that this commission is wrestling with in terms of the safe and efficacious conduct of high-quality clinical trials, and I can summarize that we must maintain high standards, both for the ethics and execution of these trials, both from a societal benefit basis, but also for our ability to bring new therapies into the marketplace that can actually be applied for the treatment of human disease.

We very much appreciate the opportunity to comment to you on the topics of international clinical trials. We commend the commission on its review. The Research Across Borders is an outstanding document that I learned a great deal on and spent more than just a few hours reading and rereading.

We presented you with written statements that I'll just give you the highlights of in this talk. I also referred you to our statement of ethical principles for BIO as well as the principles on clinical trials that in our industry, we view ethical conduct of clinical trials as inextricably linked to the quality of our clinical trials, and trustworthiness and trust is an important component of the ability of our industry to have our products accepted by the medical community and by patients. We have long supported responsible and ethical testing, protection of individual privacy, and genetic information and regulatory systems that best serve humanity and advance research into new treatments for patients regardless of where the research is conducted.

So, we support as BIO the appropriate oversight of clinical trials and medical research whether they're conducted in the United States or anywhere else in the world. We have long argued as an organization that performing important research and protecting research subjects are mutually attainable goals. BIO believes that decisions regarding whether and how to use medical products must be made with profound respect for the rights of the patients first. In our view, the appropriate regulation of biotechnology should be solidly rooted in values that this commission has outlined and that we support, autonomy, privacy, beneficence, social justice, and intellectual freedom. We have given you our statement of ethical principles. We walk the walk as well as talk the talk, and our committee on bioethics reflects the importance of the standing committee of the board of how we address bioethics as a operational and fundamental component of how our industry functions.

Now, there are several reasons why commercial drug sponsors may wish to conduct research outside of the United States, which is the focus of this meeting. When searching for potential patients, investigative sponsors reach a much larger population by conducting research both inside and outside the U.S. Finding a sufficient number of clinical sites, whether it is a rare disease or even a common disease that is intensely investigated, is a challenge now in our industry.

The ability of high-quality clinical sites and patients is a rate-limiting step now in the development of drugs in a number of important disease areas. So, our ability to recruit and conduct clinical trials at an effective rate without compromising on operational or ethical principles is important for us as we do our studies on an international setting.

We also may want to conduct trials outside the United States to study diseases that are found predominantly in those countries and not necessarily in the United States itself. And furthermore, global trials increase patient data regarding race and ethnicity and expand knowledge of racial, ethnic, and genetic variations in disease and patient care. It is true that the average cost per patient for clinical trials is somewhat less on a global scale on international trials, but that differential is rapidly changing over time, and in an economic downturn especially with rising costs, it is incumbent upon companies without compromising its ethical or operational principles to find the best price to be able to accomplish the same outcome. And therefore, we look carefully at all international trial sites that must meet very high standards for quality and for approvability from the Food and Drug Administration, but we do look for cost savings if we can, and that is true. Clinical trial costs because clinical healthcare costs tend to be lower out of the United States.

Recent press coverage has raised concerns about how clinical trials are being performed in the developing world, and some have asserted that sponsors conduct clinical trials abroad to avoid red tape or to avoid scrutiny of strict regulatory bodies such as the United States Food and Drug Administration. Let me disabuse you of that. Any research that's done by companies in BIO that have the intent of seeking FDA approval must meet extremely stringent FDA standards regarding a good clinical practice which is analogous to the common rule that the HHS is reviewing now. We cannot compromise on that because our data and our studies which represent potentially hundreds of millions of dollars in investment would be compromised if we don't maintain those high standards and are able to get a high level of regulatory review from the Food and Drug Administration.

The FDA regulations require trial sponsors to undertake quality assurance and audit activities irrespective of where the trials are conducted whether it's in the United States, in Europe, or anywhere in the world, Asia, etc. Failure to abide by these rules could delay or disqualify a product's chance of getting marketing approval, and companies develop numerous processes to ensure compliance. I think it's important that even my academic colleagues are not aware of the extent that we take, the processes that we take to ensure that we have a high-quality ethical and operationally effective program. These include standard operating procedures, training programs for the staff, pharmaco-vigilance, looking very carefully on a real-time basis on adverse events that must be reported to the FDA as they occur, serious adverse events, and disseminated to the individual review boards all over the world on a real-time basis, the establishment of independent data and safety monitoring boards that are not associated with the company that make independent decisions on the efficacy and ethical conduct of the trial and whether it should be continued or not or stopped early. We have regular sponsor monitoring of clinical trials, audits, and quality assurance units that audit operations on a real-time basis to ensure adherence of company personnel to regulations, guidelines, policies, and programs. So there are examples of unethical clinical trials performed around the world, and these tarnish the reputation of all research that's done.

For that reason, BIO takes seriously the ethical issues that other research organizations confront when conducting overseas clinical trials. There are three of them. Inducement, it's a fundamental principle that participants have voluntary, informed consent without inducement. That is also the basis for the Declaration of Helsinki of Ethical Principles. However, in some countries, there are a number of issues, socioeconomic class, literacy, etc. that would make inducement, however unintentional, a real issue in terms of defining voluntary consent. Companies must address

whether research participants or other citizens have true non-inducement in terms of giving medical care during a clinical trial in areas that don't have medical care, for example, and whether or not the citizens will provide the product after the trial is concluded. Informed consent is U.S. law. The participant must understand risk and benefits in research, in the research project. It is a bedrock principle of the regulatory system in the U.S., and BIO agrees with the commission's report. A voluntary, informed consent must be required.

From an independent oversight, U.S. law requires independent oversight by an IRB. We adhere to that as well in a serious way to protect research participants, ensure the study is done appropriately, and equivalencies must be established in locals overseas in which IRBs are not available. We take great pains to do that including putting on U.S. IRBs for overseas trials if we just simply can't get that.

We have three specific comments for the commission's recommendation. We agree that ethics training for investigators is an important element and something that will help raise the awareness and execution of ethical principles in clinical trials. We believe that professional associations, research institutions, or government programs are more appropriate and logical choices from a funding standpoint, but we recommend specifically the establishment of a multi-stakeholder group consisting of representatives of investigators, commercial sponsors, research institutions, and others to develop best practices. We all come at this with a similar goal, but different approaches. In a sense, we're two countries separated by a common language, the United States and U.K., academic research and industry research, but our goals are very similar in terms of advancing human knowledge and improving the human condition.

I think at the end, the compensation issue is probably the most important. The justification for compensation from the National Vaccine Injury Compensation Program is what's been proposed, the justification erased on the notion that immunization is socially collaborative. We agree that social good is served by this, but we have some concerns with this proposal that we just want to highlight. It's correct that this has been a successful program, but it was created to compensate injured citizens quickly and fairly, but outside of the tort system, I think that's an issue that should be addressed, but the most important point here is that a new compensation system that's being applied for government research may duplicate or undermine alternative solutions that already exist. You should be aware that in the private sector, sponsors are required to obtain clinical trial insurance to pay for medical expenses for injured trial participants. These are very expensive programs that we engage in, in any clinical trial, both in the U.S. and internationally. We recommend that a clinical trial insurance approach be explored as the solution for public sector and academic research.

So, while we have many reasons for clinical trials being performed, our goals are to have high-quality, highly ethical clinical trial data that is trusted and trustworthy that will pass FDA review and that will be accepted by the clinical community and by patients for the treatment of disease. BIO looks forward to working with this commission as well as regulator researchers and others to develop the appropriate ethical frameworks that protect patients while facilitating important research.

Thank you for the opportunity to speak today. I am happy to answer any questions.

Amy Gutmann: Thank you, and we'll hear questions after we hear both presentations. Our next speaker is Jeff Francer. Mr. Francer is assistant general counsel of the Pharmaceutical Research and Manufacturers of America, also known as PhRMA where he provides advice and advocacy on FDA regulatory and policy matters. Mr. Francer also advises and participates in the committees that draft

PhRMA's code on interactions with healthcare professionals, also known as the PhRMA Code, its principles on conduct of clinical trials and communication of clinical trial results, and its guiding principles on DTC advertising. Mr. Francer formerly served as associate chief counsel in the Food and Drug Administration, FDA, from 2003 to 2005, so he's seen this from both ends so to speak. Welcome, Mr. Francer.

Jeffrey Francer: Thank you so much, Dr. Gutmann and distinguished members of the commission and staff. PhRMA is pleased to provide additional testimony today to supplement our written comments submitted to the docket in May of this year. PhRMA represents the country's leading pharmaceutical research and biotechnology companies. In 2010, PhRMA members alone invested 49.4 billion dollars toward discovering and developing new medicines. PhRMA and its member companies are firmly committed to conducting high-quality, scientific, and ethical clinical research in a manner that respects the rights, dignity, safety, and welfare of all research participants wherever in the world clinical trials are performed.

In my testimony today, I will focus on three areas. First, PhRMA's support of educating clinical investigators on the value and rationale that support the very complex human subject protection laws and regulations in the United States. Secondly, PhRMA's support for harmonizing human subject protection regulations both in the United States and globally. Third, support for government funded coverage of injuries that result from government funded clinical trials in providing by way of example the typical practice of reimbursement for injuries caused by investigational drugs and trials sponsored by PhRMA's member companies.

First, PhRMA commends the commission for initiating an extremely thorough review of the current rules and standards for protecting human subjects in government funded scientific studies in the wake of the revelations regarding government funded research in Guatemala from 1946 to 1948. We agree with President Obama who observed that these revelations offer a sobering reminder of past abuses. While the United States government's past support of unethical research in Guatemala in the 1940s is shameful, we're happy to say that it does not reflect the current regulatory regime or current industry or government practices. The existing standards for human subject protection are significantly different than those during the time that the Guatemala research was conducted and PhRMA agrees with Secretary of State, Hillary Clinton, and Secretary Kathleen Sebelius that the regulations that govern U.S. funded human medical research today prohibit these kinds of appalling violations.

In order to help ensure that future government studies do not repeat abuses such as those that occurred in the Guatemala studies, PhRMA supports enhanced educational efforts aimed at future clinical investigators around the values behind today's complex rules and regulations governing clinical research. In 2002, PhRMA adopted its Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results or the PhRMA Clinical Trial Principles. I have a copy here which I'm happy to provide to any members of the commission, and it's also available on our website. These principles, which are based on standards established by the Declaration of Helsinki and the International Conference on Harmonization's Guideline for Good Clinical Practice, reinforced the biopharmaceutical industry's commitment to the safety of research participants, and as mentioned previously, many of these standards go well beyond federal requirements including in the areas of transparency of clinical trial results. I urge you to take a look at these principles.

PhRMA believes that government and private sponsors could use materials such as the PhRMA Clinical Trial Principles and perhaps other co-developed materials as resources for enhancing the training of clinical investigators and enhancing the profession of clinical research.

PhRMA would be happy to work with the Department of Health and Human Services in designing and implementing such a program.

Second, I would like to discuss PhRMA's support for harmonizing human subject protection regulations. The development of innovative therapies to treat disease and improve the quality of life is a long and complex process that is fraught with risk. It takes on average 10 to 15 years and more than 1.2 billion dollars to bring a single new medicine to the market. Moreover, only one in 5,000 to 10,000 compounds identified in the lab makes it through the development process and obtains FDA approval. Inefficiencies in the development process including non-harmonized regulatory requirements can increase the time it takes to develop new medicines as well as potentially increase the number of research subjects required in a global development program.

The majority of the clinical research conducted by biopharmaceutical companies in the United States is governed by regulations adopted by the FDA. The FDA has promulgated comprehensive regulations governing the clinical trial process including the requirements for submitting and maintaining an effective IND, the requirement to obtain approval from an IRB, and the requirement to obtain informed consent from study subjects. Together, these regulations often are referred to as good clinical practice or GCP requirements.

In addition to the FDA's regulatory regime, HHS and 14 other federal departments have signed onto the common rule. As discussed in PhRMA's earlier comments, these GCP requirements are comprehensive and serve to protect the rights, health and safety of research participants. Moreover, these requirements apply not just to domestic clinical investigations, but also to studies conducted in foreign countries. PhRMA supports harmonization of clinical development regulations including requirements for human subject protection. Multiple development programs to satisfy regulatory requirements in different regions of the world are not practical or sustainable, and significantly, requirements for multiple development programs may serve as a substantial disincentive to the development of the most urgently needed medicines worldwide.

In addition, given the ethical nature of human subject protection, different regulations and requirements across the federal government and around the world appear to make little sense. We note that HHS has recently issued an advance notice of proposed rulemaking regarding potential changes to the common rule. We urge HHS to ensure that the common rule is fully harmonized with the FDA's IND and IRB regulations and other global standards.

Finally, the commission's staff has asked PhRMA to provide testimony on the typical practice of pharmaceutical companies' sponsors providing compensation for injuries caused as a result of investigational drugs used in our clinical trials. To that end, PhRMA performed an informal survey of our members in order to inform the commission. PhRMA's members typically commit at the outset of a clinical trial to pay the costs of medical care provided to treat injuries incurred by research participants that are caused by investigational drugs during a clinical trial. If companies commit to provide such compensation, they may commit to pay either the cost of all medical care required to treat injuries caused by investigational agents or companies may commit to covering the cost of medical care that's not reimbursable by a third party payer. PhRMA would support government funded reimbursement for injuries that result from government funded clinical trials just as is done in the private sector. We believe that such a practice would be ethical and consistent with the typical practice among our member companies.

In conclusion, PhRMA believes that the Guatemala study conducted by the U.S. government in the 1946-48 marks a dark chapter in human research, yet robust and comprehensive federal and international regulatory standards have been enacted and implemented during the last 60

years. We applaud the commission and its staff for its thorough examination of this incident and your consideration of relevant policy perspectives to guide the future of clinical research. We appreciate your consideration of my testimony, and I'd be happy to answer your questions.

Amy Gutmann: Thank you both very, very much. Let me begin to use the chairman's prerogative to ask the first question and then open it up to my colleagues to ask others. So the commission's international research panel stated in its report to the larger commission that the principles and practices designed to protect the health and well being of research subjects should not vary according to funding source. So, I'd like to put the following two questions to you. First, do you agree? Should the ethical requirements that attach to doing research with human subjects vary or not vary depending on whether public or private money is used? And second, if, as I impute from your testimony, you're going to say it should not vary, if it should not vary, what would you say some of the implications of that are for—let me just give you the most probably complex, but also continual recommendation that comes. What are the implications for compensation in a complex federal system, should, for example—I just want to hear your views on this, should the federal government require institutions that do clinical research to have insurance to compensate victims for unintended harm consistent with our tort system?

So, two-part question: The first part is absolutely essential for our own set of principles and the second is to ask you for some comment, further elaboration on your views on compensation.

Jeffrey Francer: I can take a first stab at that.

Amy Gutmann: Sure.

Jeffrey Francer: It doesn't make sense from an ethical perspective why there would be a difference in requirements for clinical trials depending on source, and I think, you know, greater than 90% or more of the requirements are exactly the same. The common rule which applies to federally funded studies governs all aspects of federally funded research. The FDA's requirements tend to govern the commercial development of medicines and medical devices, and so by and large, for most of the requirements, there is very little difference. There is great synchronicity between the FDA regulations and the common rule regulations. There does appear to be a difference in the compensation scheme and quite frankly, I was very surprised to hear—and I learned from this commission staff that the federal government does not have a policy for providing compensation for injuries caused in those clinical trials. This is an area where I think the government can learn from the practices of private industry. I'm very happy to say that based on looking at the practices of our companies during the last several weeks at the request of the commission staff, that our companies are providing coverage for injuries that are caused by investigational drugs, and so I'm not sure it makes sense for there to be a different requirement for the federal government.

Amy Gutmann: Dr. Medford?

Russel Medford: I think Jeff has pointed out a very similar position to us. There can't be a difference in ethical standards in the conduct of human experimentation which is what a clinical trial effectively is, irrespective of the funding source. The same standards must apply. The major issue I think we face here is the implementation of those standards in very diverse circumstances, both from a clinical trial perspective, a disease indication, the type of research that's done, and the

locale in which it's conducted.

Amy Gutmann: Can everyone hear back there? Can—ok, good.

Russel Medford: I think that's the challenge, not the definition of the ethical principles or the standards. I think even in your own report, and we agree, that the aspirational standards that have been established by the Declaration of Helsinki, law, and regulations throughout the world all share the same features of high standards. Implementation, though, is the issue. I think that's the challenge that we face as we try to harmonize how we conduct trials from an industry standpoint and how the diverse academic and scientific studies that are done by 15 federal agencies under the common rule conduct their trials. In terms of compensation, Jeff and I talked about this, we were also surprised, and I've been in academia for years. I didn't realize that you don't have clinical trial insurance. You don't have a process of compensation for injury, yet that is a bedrock principle for any—for all of our BIO programs. We couldn't conduct major clinical trial without insurance.

Amy Gutmann: We should be clear about this, just for the factual record. It's not required. There are—

Russel Medford: Understood.

Amy Gutmann: Ok.

Russel Medford: But for us, it is required from a fiduciary standpoint and from an ethical standpoint. Even under the best of circumstances, with excellent execution of clinical trials, injuries will occur in the course of those trials potentially. We have a tort system that evaluates the significance and assigning blame and also tries to correct and redress the damage that was caused. That is what clinical trial insurance underwriters go through on an extensive basis when they review our clinical trial protocols, what they're addressing, the nature of the drug, the significance of the disease, the side effect profiles, the locales in which this is going to be conducted. It is something that you might want to look at in more detail if you want to apply—

Amy Gutmann: Dr. Medford, I just need to ask just again to get—to be sure we understand what you're saying. When we're talking about compensation, we're talking about compensation that would also apply—there is a tort system that exists, right? The question is do you require coverage or insurance that would exist alongside of the tort system for unintended injuries?

Russel Medford: Not the results of—

Amy Gutmann: Not the results of negligence which could go through the tort system.

Russel Medford: Yes, I'm not sure exactly how one defines that.

Amy Gutmann: So that injury that would be unintended that would not be—that compensation would not be due under the tort laws of a state.

Jeffrey Francer: Not negligent.

Amy Gutmann: Not—non-negligent injury.

Nita Farahany: So all of the reasonable standard of care has been followed.

Russel Medford: Yes.

Nita Farahany: Sometimes injuries still arise.

Russel Medford: Clinical trials—deaths occur in clinical trials. You're studying patients who are sick, and the issue is whether or not that's caused by being a participant in the clinical trial or it's a consequence of the disease process. Jeff, do you want to—you're the lawyer.

Amy Gutmann: Do you provide—do you insure and provide for and do your member organizations insure and provide for compensation for injuries that are non-negligent in nature?

Jeffrey Francer: Right, and—

Amy Gutmann: That's the question.

Jeffrey Francer: Right, and the research that we've done into the practice of our members didn't get into the mechanism of how the coverage is funded vis-à-vis insurance or not insurance. However, what I stated before was that our companies commit at the outset of the clinical trial to pay for the cost of medical care, to treat injuries that are caused by an investigational agent.

Daniel Sulmasy: But it does not need to be triggered through the court system. These can be administered—

Amy Gutmann: They're caused—so caused by is an absolute—if it's not caused by then it makes no sense. So caused by, but not—it doesn't have to be negligently caused by. Simply caused by, you will compensate.

Daniel Sulmasy: And the person doesn't have to bring a suit to prove it.

Jeffrey Francer: That's correct.

Daniel Sulmasy: So it's not a tort in that sense.

Amy Gutmann: Right.

Russel Medford: Exactly.

Amy Gutmann: I'm asking—ok, good.

Russel Medford: And our memberships overlap considerably and that's probably true.

Amy Gutmann: Thank you very much. Now, you've clearly answered the question as opposed—

Russel Medford: It's a complicated set of—

Daniel Sulmasy: No, it's a good argument.

Amy Gutmann: But the question isn't complicated, right? It's—

Russel Medford: Dr. Gutmann, it's in real time that people are injured in clinical trials. There's no time to go through a tort system for recovery of—

Amy Gutmann: I understand all that. I was asking you to say whether you provide compensation outside of what can be gotten through the tort system.

Daniel Sulmasy: A further, quick one is that I'd heard a difference here that you said this was required. Is this—if this is required, by who?

Russel Medford: Oh, in Europe, clinical trial insurance is required.

Daniel Sulmasy: In the United States?

Russel Medford: You know, I don't know if it's required in the United States.

Jeffrey Francer: I don't believe that it is.

Amy Gutmann: It's not required. It is not required in the United States.

Russel Medford: But it is required in Europe.

Daniel Sulmasy: So there's no industry standard that says everybody has to do this, etc.

Jeffrey Francer: It's just an industry standard that it occurs.

Amy Gutmann: Ok, now I'm going to move—Jim is going to take other people's questions.

James Wagner: I was going to go in another direction unless, Nita, yours is a followup to this particular point.

Nita Farahany: I want to have a followup just to make sure I understand the system a little bit better.

Amy Gutmann: Ok, [inaudible] little bit. Go ahead.

Nita Farahany: So, Dr. Medford, you also mentioned as you were talking about the difference between the National Vaccine Act compensation program, that the National Vaccine Act was outside of the tort system, preempts the tort system, I'd like to understand how the compensation

system which here it sounds like it's providing compensation at the level that the National Vaccine Act works. How does it work in conjunction with the tort system since it isn't federally mandated? There isn't federal preemption of tort, state tort law, I mean is it additive to tort suits that can be brought or does it—do people waive their tort liability in order to accept compensation for any injuries that are caused by an investigational drug?

Russel Medford: Well, Dr. Farahany, as you know, the National Vaccine Act was designed to address the concern and the issue that manufacturers of vaccines would not manufacture vaccines because they were liable in the legal system for suits. We had desperate need for the production of vaccines, and therefore, this act was put together to provide a mechanism outside of the tort system for evaluation and redress of injury. To add both together is kind of—I don't think it's double indemnity, but it defeats the purpose in a sense.

Nita Farahany: Sure. Good.

James Wagner: Going in a different direction, first of all, thank you both for your presentations and for being here. That we have you here gives us a special opportunity to, I think, ask about the dimension of commercially supported human subjects research. Russ, you mentioned that intellectual freedom is among the principles that you think are important to be applied toward ethical human subjects research, and we've seen—in the Guatemala case, we have seen a combination of scientific curiosity, being generous, perhaps vanity in hubris to be more pejorative, lead to breaches in ethical practice.

We also continue to experience, unfortunately, conflicts of interest that actually challenge the intellectual freedom, if you will, of researchers who are performing clinical trials research, you know, and the stories, sadly, continue of conflict of interest as they are—as significant sums of money sometimes are paid by industry to support these researches.

Do you imagine, and how can we avoid if you do imagine, that this sort of profit motive and the temptation for profit motive, do you imagine that in addition to scientific curiosity run amuck that these bring additional pressures that could compromise the ethics with which we expect our investigators to pursue human subjects research?

Russel Medford: I think you raise an important question, Dr. Wagner. This is a human activity, human endeavor, and human foibles are going to be pressuring us to do things that are not necessarily in the best interests of our patients or society at large. That includes profit. It also includes career advancement. There are monetary and non-monetary issues that can color the conduct of a clinical trial. I think it's our challenge as an industry and as an organization to recognize the human nature of our activity and to ensure through education and regulations and oversight that we minimize that. We can never eliminate it. It will always crop up, but—

James Wagner: And what would be a mechanism that you might anticipate to—

Russel Medford: Well, we currently have, at least from an industry standpoint, we've established as trade organizations, PhRMA and BIO, very high standards that we've set and expect our members to adhere to. We also have a single, major regulatory body that imposes those standards on us in a uniform fashion, the Food and Drug Administration. This is a tough task master. They have a tough job, and they let us know that they have a tough job, so we spend most of our time trying to

reach the standards that they have to set. That's also an example for HHS in trying to harmonize the common rule across 15 different federal agencies. In our case, we have one federal agency that's responsible for interpreting essentially the common rule. In their case, they have 15 agencies that are interpreting it, so I think we can learn from many years of experience and many thousands and hundreds of thousands, if not millions, of patients that have been investigated now in clinical trials from the industry on how one implements these ethical principles and minimizes the issue of conflict of interest.

The last point I'd like to make, though, is the industry and academia are joined at the hip whether we like it or not. We need academia to advance our science and to bring new products to the marketplace. Academia needs us for our expertise in being able to translate that science into practical application that can be applied and trusted by the clinical community and by patients. If we cannot solve the conflict of interest issue that is separating our two areas, we're going to fail as a country being innovative in medicine.

James Wagner: I agree.

Amy Gutmann: Thank you. Dr. Michael?

Nelson Michael: This is a question really for both of you, but it stems from comments that Dr. Medford made. You went through a very cogent and thorough discussion of what you would consider to be important frameworks to ensure the ethical conduct of trials to include GCP and SOPs, pharmaco vigilance, DSNBs, etc. I was wondering what your thoughts would be, your collective thoughts, about the—what industry's perimeter is on looking at research safeguards from the other direction, in other words, the formation and the cogent inter-digitation of community advisory boards, the use of good participatory practice guidelines or other normative body guidelines, your thoughts about the onus on industry to increase the resource absorptive capacity when you work overseas or even in the United States, your thoughts about tech transfers, so all the things that would accrue to essentially leaving the site where you work a better place and ensuring that all the good things that you talked about are, in fact, vetted and agreed to by other members of the research stakeholder community.

Jeffrey Francer: I can take a shot at that. I think our companies are committed to working with the communities where they exist. In the United States, frequently, there's community input through the IRB, and under U.S. law, there has to be non-scientists, there has to be a certain amount of diversity within the IRB, and I think that we have to make sure that the industry is cognizant of the communities where they practice.

Amy Gutmann: Dr. Medford?

Russel Medford: I'm in agreement. I like your term you leave the place a better place. You know, you police your place and you leave it better than where you left it. We endeavor to do the same thing in all the areas that we do clinical trials, and where possible and appropriate, we try to address the disparities that would be relevant to the communities, the local communities. We cannot be the sole purveyors of correcting social injustice and global inequities as an internationally active group. Nevertheless, in our specific worlds, we can improve medical education and medical care and access to the best that we have from medical science.

Amy Gutmann: Dr. Atkinson?

Barbara Atkinson: I'm interested in the harmonization that ANPRM talked about it, but many of the people that commented on that, it was mostly the adverse events that they commented on and how difficult it would be actually harmonize anything, and I'm wondering what areas you thought were going to be the most important to harmonize and probably the most difficult to harmonize, both in the U.S. and worldwide.

Russel Medford: Well, we've spent many years at our level on the international conference on harmonization to harmonize European regulatory rules with the FDA. We've made recommendations, for example, on audits. The FDA audits our clinical trial sites. They establish are your international sites actually adhering to our standards. EMEA has very similar standards, and so our proposition is to combine those two processes to broaden, share the data, and auditors from Europe will be able to share their information with auditors from the United States.

Barbara Atkinson: Has that happened?

Russel Medford: Well, we don't know actually. I don't know if that's happened or not. Right now, we get audited by the FDA, our clinical sites, our manufacturing sites are all audited by the FDA. We haven't seen—except we get European audits when we're under European Medicine Agency standards. But in terms of what the difficulties of harmonization are, the analogy that I made to Jeff actually this morning and perhaps it's before I had my first coffee is it's an interstate train system that no one's agreed on the gauge of the tracks. We all know that we're going by train. We all know we want to get from the east coast to the west coast, but we have different gauge tracks, so therefore, you have to stop your train going from New York to Chicago, unload everything, and then put it onto a new train with new tracks to get to Denver, and then the same thing to go from Denver to Los Angeles. That's how I see the issue that we're facing with the harmonization of the common rule and 15 agencies on implementation, but there is a similarity on a global scale as well. It's the implementation process.

The last analogy is the multiple types of insurance claims one has to fill out for medical reimbursements. It's the same information, but all formatted differently with different emphases. So we spend a great deal of time and effort, our investigators, in terms of redoing, rewriting, or reinventing the wheel each time as we want to advance a program forward. So harmonization is implementation across the board. It's not just adverse events. It's efficacy, ethics, etc.

Amy Gutmann: Yeah. Thank you. Dr. Arras? We're not going to be able to get to all the questions, everybody has them, but I will go over five minutes, but let's, us, keep our questions brief. Yes?

John Arras: Thank you for your testimony this morning. One focus of this session is supposed to be the extent to which research norms are viewed as obstacles to business as usual and the extent to which they're really internalized as professional standards. We've talked so far about the pharmaceutical industry's efforts in this direction and also about academia. There's a third group that hasn't been mentioned yet which is the CROs, the contract research organizations. Could you say a bit about their role in this process and, you know, what contribution they make to the

professionalization of ethics? Because they're like, you know, one, you know, level down on the food chain here, and I'm wondering what sort of affect their existence has on this overall problem.

Jeffrey Francer: Sure, and I think you bring up a very important point. The industry has set forth a set of principles. The United States government has set forth a set of principles and governments around the world have set forth a set of principles on the proper way, the ethical way, to conduct clinical trials. It's up to us, it's up to industry leaders, it's up to the government to make sure that those principles filter down to their agents so that at the end of the day, when the work of this commission is done that the learnings of the commission and the report of the commission enter into curricula, I think both for government research as well as private research and filter down through the agents.

Amy Gutmann: Dr. Sulmasy?

Daniel Sulmasy: Another very specific question for Mr. Francer. Putting aside the kind of, if you will, research malpractice insurance which I think is what Dr. Medford was really talking about, concentrating back on the compensation for subjects who have been harmed in the conduct of research, you mentioned there were two ways of doing this, sometimes either paying all of the medical costs and secondly, sometimes paying on top of—for anything that wasn't covered by the patient's own private medical insurance. My question is what's the mechanism for paying those costs? Is that simply borne by the company itself as the cost of research or do they have some sort of health insurance system for subjects in research?

Jeffrey Francer: I think that the short answer is every company's going to do it differently. You know, the interesting, I think, aspect to this is that depending on what type of health insurance a person has, he may or not have primary coverage as a result of just going through your normal insurance, and so the short answer to your question, unfortunately, is that every company will do it differently.

Amy Gutmann: I have two questions from our participants, and they're both on compensation, so I think this will help us, I think, really clarify from your perspective what's going on in the private sector, ok? So, and I'll ask the members and our participants to stand up so we can recognize you. Pablo Delora? Thank you. Pablo is in the Harvard Ethics and Social Health program and is a visiting professor, and this is regarding compensation.

The question is in the context of clinical trials, why shouldn't we say that non-negligent harm that is caused, the non-negligent harm that is caused, why shouldn't we say it's covered by the consent of the subject? Or should we say that it's covered by the consent of the subject?

Jeffrey Francer: It's a—I mean, I think it's a very interesting question, and it's important to recognize that clinical trial subjects are taking on risk when they enter into a clinical trial. I think we have a set of norms in our industry that when there's injury that's caused by investigational agent that harm will be covered, and of course, clinical trial subjects can receive great benefit from clinical trials and they obviously take on some risk, but our system is developed in the way that we've described.

James Wagner: I wonder if our questioner isn't imagining if there might be three categories of

injury. One is negligence and we've done with that. The second is when someone says, "Now, this could result in a loss of hearing," and you sign consent to that and, in fact, the loss of hearing takes place. The third category is something that's unanticipated, but non-negligent, an allergic reaction or something like that. I believe that's what is being asked. Do you believe—

Amy Gutmann: I think it's broader than that. I think it's actually saying human subjects consent to research and don't they consent to everything that's non-negligent that happens as a consequence of that research. That's a position that requires a response.

Jeffrey Francer: That's a position. I don't think it's the dominant position, but it's certainly a position one could take as a matter of philosophy.

Amy Gutmann: Yeah. Dr. Medford?

Russel Medford: Yeah, I think you raise an important issue. It's the issue also of clinical equipoise and the contribution that patients have when they subject themselves to clinical trials. They—remember, they confer—they receive benefits as being part of the clinical trials, yet they also receive also some risks. Non-negligent harm, as Jeff pointed out, I think, is something that is applied by individual companies. I think a broader interpretation of that—I mean, one can—one has to define those terms because one could say that the conduct of clinical trials implies support of a healthcare system for every individual that's in a clinical trial forever. That's possible, too, and in fact, society could demand that. The consequences of that, though, might be negative in terms of clinical trial execution.

Amy Gutmann: So let me ask the next question. These are questions from members of public audience, remember.

Russel Medford: I got it. I'm just—I'm trying to answer as best I can.

Amy Gutmann: But they're all very excellent. So this gets to what you just said. Can you clarify compensation payment for medical care cost is not the same as payment for injury such as lost wages? We're talking about the former. Correct? In other words, for medical care costs rather than lost wages.

Jeffrey Francer: That's my understanding.

Russel Medford: That's mine, too. But I'm not an expert in that. I'd have to dig into that.

Amy Gutmann: Ok, this opens up the question of how broad or narrow compensation should be, and we're going to have more time to discuss this, but the basic answer that you're giving as far as what's going on in industry is that there is a system for—or at least practice across industry of compensation for non—some compensation for non-negligent harm.

Jeffrey Francer: That's my understanding.

Amy Gutmann: One more and then we will break.

Raju Kucherlapati: Thank you very much for your presentation. I want to ask a different question. Between the two organizations that you represent, I assume that, you know, you cover a very large proportion if not all of the commercial activities involving human subjects research, and I want to ask the question about research that is done outside the United States. Both of you have addressed this issue, but despite the comments that you have made, there are people who have come before this commission who have articulated the view that the major reasons why pharmaceutical companies or biotechnology companies go outside the United States is to reduce the cost, to be able to ensure that the regulations are much simpler than what exist in the United States, and three, that there are certain types of trials that the companies cannot conduct in the United States and that the only reason that you go outside is that you can conduct such trials that would not be considered to be ethical or appropriate in the United States. So can you, each of you, make a categorical statement about the intentions of going outside the United States and whether the statements that I have made are accurate or inaccurate?

Russel Medford: Well, let me—

Amy Gutmann: Dr. Medford, you began to answer that question. I think it's really—it's a very important question for both of you to answer because as Dr. Kucherlapati said, we heard this not once, but repeatedly.

Russel Medford: Well, let me just say that from BIO's standpoint and from my own personal experience in the industry, there is no compromise on ethical or quality issues when we identify and execute on a clinical trial site outside the United States. That is not an option. That is not part of our criteria in deciding where to do our clinical trials. We must meet the highest standards, and there are no compromises. It's an irreducible minimum for us.

Secondly, in terms of simpler regulations, well, let me answer the better question. Less cost? Absolutely. We have a responsibility of getting a high-quality result for the cheapest price. Thirdly, simpler regulation? I don't think then that your commentator understands—it's often much more complicated to do clinical trials outside the United States from a regulatory standpoint. It is not simpler in most of the areas that I've ever been involved with which includes India, China, Eastern Europe, Russia, etc., and Latin America. I think that the implication—I think it's important that you recognize that it's an irreducible requirement that we have the highest ethical, operational, and data quality standards irrespective of where we conduct our clinical trials.

Jeffrey Francer: I agree, but—

Raju Kucherlapati: [Inaudible] last point about the nature of the trial that could not be conducted in the United—

Russel Medford: Oh, you know, trial, you know, clinical equipoise. You don't conduct clinical trials if you haven't addressed and are comfortable with the risk-benefit tradeoff and the information that you have. What's the potential benefit given the potential risk to individuals who are being conducted? We do that all the time. That's the first decision. All this other stuff is after you've made the decision that there's a benefit potentially to be gleaned. So you cannot conduct a trial that doesn't meet that criteria of clinical equipoise. In my opinion, I think from a BIO opinion as well.

Amy Gutmann: Mr. Francer?

Jeffrey Francer: I agree with Dr. Medford. You asked, you know, is the primary impetus or is the only impetus cost or less standards. We're in an industry and in a world that's harmonizing its standards, and I echo the point that no matter where a clinical trial is done, if it is for licensure in the United States, the FDA is rigorously looking, and even more so now than before, at the clinical trial data, individual data. Secondly, one last point, we make medicines that are used globally. Is it ethical to only test them in the United States? I don't think so.

Amy Gutmann: Thank you very much. This has been an extremely helpful and enlightening session. Thank you. I ask everyone to thank our two presenters. We will take a five-minute break and reconvene at 10:45.