Introduction – 1:04

My name is Jeff Cooper and I'm the Chair of the Institutional Review Board at Albany Medical Center. And today, what I want to go over are the basic ethics of human subject research.

In my talk, I've gotten a lot of ideas from several people, from Bob Levine at Yale, from Lawrence McCullough who's a bioethicist at Baylor University and also from John Nance who is a pilot for Alaska Airlines and also the ABC flight correspondent.

The objectives of this course, at the end I hope that you'll know the basic ethical principles of research governing human subjects, understand the ethical basis of the federal regulations.

And in this, I'm going to mix and jump back and forth between the ethics that we have to deal with and the history that we have to deal with.

The reason is because I think that by looking at the history, it helps place the ethics that we have in some sort of perspective. And in addition, the ethics help explain what kind of problems that people were trying to solve as they came across certain historical issues.

In addition, it's also been said that those who fail to study history are condemned to repeat it. And I've been asked to remind you that those who fail to study this course are condemned to repeat it as well.

Ethical Decision Making – 5:31

In this module, I'd like to go over ethical decision making. What is ethics and what is morality? Well, ethics is the disciplined study of morality. And morality asks the question what should one's behavior and character be.

There's a couple of different kinds of ethics. There's ethics called descriptive ethics and this asks the question what are the moral beliefs and practices of an individual or groups of individuals or institutions or society. This is really an anthropologic question.

It's not the question that we're very much interested in when we're doing applied research ethics. What we're interested in is what's called normative or prescriptive ethics. This branch of ethics asks these kinds of questions. What ought morality be? How should you as researchers behave? How should you as researchers not behave? What sort of character traits should you cultivate as virtues and what sort of character traits should you avoid as vices?

And I think the benefits of this, I want to give you a framework so that you'll have some sort of structure for analysis and decision making when you come across issues that you find in your
research. And hopefully, by doing that, help you avoid some snap decisions by giving you an opportunity to do some reflection and make some better decisions.

Now, there are two types of ethical decision making that you might come across and that you will probably actually do. And one is deductive or principle based reasoning and the other is inductive or case based reasoning. And I'll go over each one of these.

In deductive reasoning, we start with a particular ethical theory. And there are a number of ethical theories out there. You might have heard of them. They're called things like libertarianism, utilitarianism. The particular ethical theory is not that important because most ethical theories come down to various similar sorts of principles and rules. But from these ethical theories, we have specific principles. And from those principles, we develop rules. And from those rules, we make particular judgments.

For example, you might have an ethical theory that says that peace is an important principle in your life. And so from that, you might make the rule that violence never solves anything. And from that, when the government comes to you and says we're going to hold a draft and we're fighting a war and we want you to fight in this war, you might say, "I refuse to join the Army." Now you can kind of get an idea about how old I am here.

So let's look at case based reasoning. With case based reasoning, we all make decisions in our lives and we have a history of the decisions or the precedents that we've made. And so when we're doing case based reasoning, we look back at those previous decisions and we combine them in order to make a particular judgment. And those particular judgments then reflect on our rules which then reflect on our principles and reflect on our ethical theory.

For example, you might be in a situation where after deciding that you're not going to join the Army, you move to Canada and suddenly the United States decides to invade Canada for some reason. And now you find that you're defending yourselves. And so you might say I'm going to join the Army. Why are you doing that? Because you say I must protect my children. That's an important part of my life. That's a rule that I have in my life. And perhaps that rule reflects on your principle that family is very important to you. And then that would reflect on your ethical theory.

You might have heard the definition of conservative is a liberal who's been mugged. Have you ever heard that one? So just to show you that I have no particular leanings towards any political stripe, a liberal is a conservative who's been indicted. I don't know. I'm still trying to figure out where that places President Clinton.

The important part of this is that we may hold certain ideas in our mind of principles and framework that we use to make decisions based upon underlying principles, in this case conservatism versus liberalism. But then reality may come along and they slap you in the face. And suddenly you look and say, "Wow, this is not consistent with other things I've done in my life. I have to think of something different." And that then changes your decision making and changes your framework for the future. So this is really an example of these jokes are really based upon the conflict between principle based reasoning and case based reasoning.
So I gave you two ethical decisions that we made. In one method, we said we're going to refuse to join the Army and another one, we said we're going to join the Army. And what ethicists would say in this case is that we have conflict obviously between our decisions. Now, when ethicists see conflict, they don't stop at that particular conflict. They go back and they ask themselves what were the principles that were used to make these particular decisions? And a lot of times you find, like in this case, you have fairly Mom and apple pie type of principles that went to come up with fairly conflicting decisions. Principles like peace and principles like family.

And what ethicists would say is that these two principles are incoherent. And it's important when you come up and you see decisions where people are arguing about whether we should choose one decision or the exact opposite decision and people are making those arguments, to go back and look at the principles. And ask yourself what are the principles behind what people are saying and what's the incoherence behind those principles?

So in summary, ethical decision making is both principle based and case based. We've used both types of decision making and I think it's inappropriate to say that you have to make decisions one way or another. You're going to end up making decisions both ways. And that you're always going to have conflict in ethical decision making. And actually I think that's one of the interesting parts of ethics is the fact that nothing's cut and dried. We have situations where we have decisions where people are in conflict. But when we have those, we should go back and look at the principles and strive to force some coherence behind our basic principles. Figure out what the difference is that we're dealing with and try and come down to the specific issues of those principles that help resolve those conflicts.

**The Belmont Principles – 5:30**

In this module, I'm going to talk about the Belmont Principles which are the fundamental principles underlying the conduct of human research.

The Belmont Principles came out of the National Commission which was started in 1974 by the Federal government. And these were a group of people where the government said, "we want you to go back and identify the basic ethical principles that underlie the conduct of human research."

Now, they were asked to look at the literature, to look at the arguments that people had made, to go over what were ethicists saying about research up until this point. And we knew that there were a lot of particular judgments, that people made rules. But they were asked to say well, what were the fundamental principles behind the decisions that people were making.

In addition, they were also asked to develop guidelines to assure that human research could be conducted in accordance with these principles. And these guidelines in the end came up to be the current set of federal regulations that we have. And this led to the Belmont Report in 1979.
And so from the Belmont Report, they came up with three fundamental principles underlying human research. And we call these the Belmont Principles because they came from the Belmont Report. And they are respect for persons, beneficence and justice. And I'll go over each one of these.

Respect for persons says that we should treat individuals as autonomous agents and that we should not use people as a means to an end and that we should allow people to choose for themselves. And if we have people who have limited autonomy and have an inability to choose for themselves, we should provide them with additional protections. Basic idea of respect for persons.

Principle of beneficence is that we should have acts of kindness that go beyond charity, that go beyond duty. This is really more than being a nice person. This is really going out of your way in order to do nice things for other people. And from the principle of beneficence, we have various obligations that are familiar to us in medicine. Things like do no harm, prevent harm, prevent evil, promote good. These all come out of the idea of beneficence.

And the principle of justice gives us the idea that one, we should treat people fairly. And secondly, that there should be a fair sharing of the burdens and benefits of research. We should not burden one group with the risk of research in order to give another group the benefits of research. This is the idea of justice. And I want to sort of make a distinction here between procedural justice or the process of procedural justice and what we're talking about, which is distributive justice.

People think of the court system commonly when I talk about justice. And the court system is the process of procedural justice. It is a way that there is a fair system when people are in conflict that they can resolve that conflict. Now, it doesn't mean that the decisions that come out of the courts are necessarily fair to society in whole and you can see that with malpractice suits. The people who sue get the benefits and the people who don't sue don't get the benefits. So some people get windfalls and other people don't. So the system is not necessarily fair in a distributive sense, it's fair in a procedural sense.

What we're interested in research is not the issue of procedural justice, but the issue of distributive justice. When we're doing research, we want to look at society as a whole and make sure no one group is taking the burdens and another group taking the benefits.

The kinds of derived rules that may come from these principles, again we talked about that we have basic principles and from those, we'll derive rules. And the rules that we derive from beneficence are the idea that we should have good research design, competent investigators and a favorable risk/benefit analysis. Because if we don't have this, then we're not doing kind and charitable things for other people by subjecting them to bad research or incompetent investigators or situations where the risks outweigh the benefits.

From respect for persons, we get two important concepts. One is the idea of informed consent. And that is, if you're going to have somebody participate in research, you want to give them a
choice. Ask them whether they want to participate. Give them the information. Let them make the choice.

The second issue that we get from respect for persons is that we are respectful for people's personhood when we respect their privacy. When they have things that they tell us that they do not want shared with others that we ensure that it is not shared with others. And we can do that either through the process of confidentiality which is the solemn pledge that if somebody tells us something that they don't want shared, we're not going to share it.

Or through anonymity and that is the information that they give us will be recorded in such a way that nobody will be able to look at that information and figure out who that came from, who's private information that was. And it's important because there's a difference between confidentiality and anonymity. And anonymity is really a stronger protection of privacy then is confidentiality.

And from justice, we get the idea that there should be equitable selection of research subjects. We shouldn't select one particular group that might get the burdens or not get the benefits of that research.

Now in the Belmont Principles, we have conflict. For example, from the concept of respect for persons, we have the concept that we should protect those of limited autonomy. That's a rule that we can derive from the principle of respect for persons. And from that, we could say well what do we do with children? Children have limited autonomy. They can't necessarily make competent decisions for themselves, so what should we do?

Well, the principle of respect for persons might say that we should limit their involvement in research if they cannot make the decision. But the principle of justice says that we should fairly share the benefits of research. And if we're not doing things like say testing drugs in children, then children will not have the benefit of the knowledge that we gain so that we can use those drugs appropriately in children. So the principle of justice might say we should promote research in children.

So here we have two conflicting decisions. Do we limit research in children or do we promote research in children which come from the principle of respect for persons and the principle of justice. And again, this is an issue where we have conflict in decision making with the Belmont Principles due to incoherence between respect for persons and justice.

Now the Belmont Report talks about this and the Belmont Report says that the conflict is expected. We're going to have situations where reasonable people look at the principles and come up with diametrically opposed opinions. That will happen. But the important thing is that when we see that, that we should understand that the underlying principles behind those two decisions had equal moral force. That we should not be in a situation where we say respect for persons always outweighs justice, so therefore we're always going to limit children's involvement in research, for example.

And the burden that you have as investigators and IRB's also have is really to say that we just...
have to look carefully at these principles, to look at the individual situations and really tease out when is it that we should limit research in children, for example, and when is it that we should promote research in children. So whenever have these conflicts, we have to go back to our principles and tease them out.

And one mistake that I see investigators make a lot is that they place the principle beneficence above the other principles of informed consent and justice. A lot of times, people say, "this is so beneficial for this subject, why is it that I have to get informed consent? Why is it that I have to bother with this? I'm doing such good for these people." And I think this is really a situation where investigators are placing beneficence above other principles. In research, we have to make sure that the three principles are put on equal footing with equal moral force.

**History of Research Ethics – 17:43**

I'd like now to go over the history of research ethics and give you an idea of where we came up to the Belmont Report and the Belmont Principles.

A good place to start is in the 1940's with the Nuremberg Code. The Nuremberg Code came out of the Nazi's Doctors Trial and this was a supplement to the Nuremberg Trials that looked at the war atrocities. And it's important to understand that the Nuremberg Code was written as part of the judgment. It was not something that existed before the trial. It was something that the judges and the prosecutors looked at and said it's unusual here, but we really don't have a good standard for what is appropriate in research in order to decide whether or not these Nazi doctors did the right thing or the wrong thing. It's pretty obvious they did the wrong thing, but how do you decide that?

So in the end of the judgment, the Nuremberg Code was written. And in the end, I think it's important to point out that the doctors were convicted of being murderers. They were not convicted of being bad researchers, although commonly you'll see people say that the Nazi doctors were tried for their bad research or whatever. But it was really that they were convicted of murder. That's how I think problematic the research was that they did.

Now, the Nuremberg Code has multiple principles to it. I'm going to summarize those principles here. And I would say the Nuremberg Code is essential reading for everybody involved in human subject research.

Nuremberg Code first says that the voluntary informed consent of the individual subject is essential. It then says that the research should yield useful results, that you should base research on prior animal work, that the investigator should take every step to avoid physical and mental suffering of the subjects. That when you conduct research, there should be no a priori expectation of death or disabling injury from that research.

That the risk of the research has to be outweighed by the importance of that research to the individual and to society. And that the subjects must be protected by the investigator from any further injury that might occur. That only qualified scientists should conduct research. That
subjects may withdraw at any time without penalty or loss of benefit. And that investigators must be always ready to withdraw subjects from trials who are experiencing excessive injury or harm from that trial.

Now, if you look at the Nuremberg Code, we start to see principles like having voluntary informed consent or ideas like subjects may withdraw, which come out of the principle of respect for persons, that you give people a choice. They are free agents. They can do what they want.

And we have ideas that we should base research on prior animal work, that there should be useful results that should come out of research, which are ideas of having good scientific design, a rule that we said came out of beneficence. Ideas that there should be no expectation of death or disabling injury or that the risk must be outweighed by the importance or benefit of the research. And we see the idea of the risk/benefit analysis, minimizing risk in research, a rule that derives from beneficence. So as we look back at the Nuremberg Code, we begin to see some of the basic rules and the basic principles being developed in this particular document.

What did the Nuremberg Code do? Well, unfortunately, in the United States and mostly throughout the world, it had no effect on research. Why is that? Well, the medical profession really thought that the Nuremberg Code was implicit, that most US physicians really understood what their obligations were to their subjects and the Nuremberg Code was something that they didn't really need. In addition, a lot of people looked at it and said this is really a description of criminal research. It was a document used to convict Nazi doctors as opposed to a document that really is a working document that we can apply. And a lot of people said also (which is true) it was created after the fact to convict the Nazi doctors.

The other important issue is that the Nuremberg Code does miss a lot of important aspects of research. If you think about it, the first principle of the Nuremberg Code says the voluntary informed consent of the individual is essential. Period. No exceptions. What does that mean about doing research on children? What does that mean about doing research with people who have Alzheimer's and don't have the capacity to decide for themselves? Do we say that they can't be involved in research? That's what the Nuremberg Code says.

So the Nuremberg Code is incomplete to some degree. People recognized that and that was another excuse that people used to ignore the Nuremberg Code. And it wasn't really until about twenty years later that the Declaration of Helsinki was written, which was done in 1964 by the World Medical Association.

And this was very important because this was a group of researchers getting together and physicians getting together and deciding we do need rules. We need some sort of document to guide us on what is or is not appropriate in research. And so the Helsinki Declaration represented in a way a reinterpretation of Nuremberg.

Now unlike Nuremberg, we have a document that provoked a reaction by the medical community. How do we know that? Because this is the time that you start looking in journals and you look at the instructions to authors. And you see the journal editor say if you want to publish your paper involving human subjects in our journal, you have to write in there in your methods
that you abided with the Declaration of Helsinki in the conduct of that research.

At the same time, we had a change in Public Health Service policy. The Surgeon General and the head of the National Institutes of Health realized that the government was spending more and more money on human research and was basically giving money away with no strings attached, in terms of how that research was conducted. So they said we have to have some sort of policy.

So they wrote a policy that said that if you have Public Health Service funding (like NIH funding) to conduct research, that you would have to have your research undergo prior review by an independent committee for three things. And one is that committee would have to determine that you were adequately protecting the rights and welfare of the subjects, that you had a process to ensure appropriate informed consent for those subjects and that that committee determined that the risk/benefit ratio of your particular research was acceptable.

And this in 1966 was the beginnings of the IRB. And in my institution at Albany Medical Center, this was really when our IRB was first founded. Before there were federal regulations, it was just a Public Health Service policy.

So now we have an era of standards. We have a situation in which we have the Declaration of Helsinki and we have Public Health Service policy and now we have a way that people can make some decisions because we have standards that are accepted by researchers. But maybe better, maybe worse, we have standards that can be accepted by the media. Until this time, newspaper reporters who looked at research that was done in the 1950's say really had no place to look for an accepted scientific standard as to the ethical appropriateness of that research.

And so this leads to a period of time where we have judgment. And we have a series of media exposes and physician exposes that occurred.

One of the important physician exposes, again I think excellent reading for all researchers and all members of IRB's is the Beecher article. This is an article by Henry Beecher that's called Ethics and Clinical Research that appeared in the New England Journal of Medicine in 1966.

Henry Beecher was an anesthesiologist at Harvard Medical School and he collected unethical research. He liked to look through the literature, see what was there. And he had a couple hundred cases of what he felt were very inappropriate research that was conducted and published in the literature.

And he went to the Journal of the American Medical Association and he said, "I'd really like to publish this list. I want to show people what rampant problems are out there.” And the editor of the Journal of the American Medical Association said, "Forget this. I'm not touching this with a ten foot pole.” So he went to Franz Inglefenger who was at New England Journal at the time and Franz Inglefenger said, "look, you've got too many, Henry. But if you cut it down to just a handful of articles, say twenty- two, we will publish it."

And so he published the article, twenty-two studies, all of which were performed unethically. He
did not include any references to protect the guilty. And all of these articles are important. They were published in major journals. They were published in respected journals. They were done by respected researchers. A lot of the research that he published was done by chairs of departments at major institutions around the country. They all had questionable study design and they all had limited or no informed consent.

And examples of these are that he cites two placebo control trials for penicillin for strep throat at a time when we knew that if you gave people penicillin that you prevented the non- suppurative complications like rheumatic fever. And so people were compared between either penicillin and placebo or penicillin and sulfanilamides. And lo and behold, at the end of the research, they found that the people who were on the ineffective drugs had a high incidence of rheumatic fever. And they published this.

There was another article where in an anesthesia department, they wanted to see what the effect of high levels of blood CO2 or a high PCO2 was on arrhythmias in the heart. And so they took people who were undergoing cyclopropane anesthesia, they would induce the anesthesia and they were deliberately underventilate them or actually inject them with solutions containing high amounts of carbon dioxide so the carbon dioxide blood level would go way up.

And lo and behold, these people had premature ventricular contractions and they had bigeminy and they had runs of unsustained ventricular tachycardia and they had sustained ventricular tachycardia. And they would watch these people for twenty minutes while their heart was having these life threatening arrhythmias. And they published it. No informed consent. Just decided we were going to do this because it was interesting.

There was another case, very sad case where there was a mother who had a daughter who was dying of metastatic melanoma. The researchers went to the mother and said, "We want to cure your daughter. The only way we can do this is we've got to take a piece of melanoma off of your daughter and we want to graft it onto your arm." And the mother said, "OK." She did that. The daughter died four days later. About a month and a half later, the melanoma had engrafted in the mother and they took it off. They did a wide resection. The mother died of metastatic melanoma a year and a half later. And they published this.

So this provoked a big reaction in the community. People really took this to heart. And I like what Bob Levine said about this, that until this article, we assumed that unethical research could only be performed in a depraved regime like the Nazis. And here we were in the United States, this literature just got published and nobody said anything about it until Henry Beecher wrote this article.

There were a number of media exposes here. The Thalidomide Trial, the Jewish Chronic Disease Study, the Willowbrook Hepatitis Study, the San Antonio Contraception Study, the Tea Room Trade, the Milgram Study and the study of untreated syphilis in black males. Things that the media detected and published and created a great outcry. I don't have time to go over all of these.

In Bob Levine's book on Ethics and Regulation of Human Research, there are great descriptions of each of these studies. I'm going to talk just about the Tuskegee Study, the last one, because
that's a study that lead to the eventual formation of the National Commission and the Belmont Report. And I'm also going to talk about the Milgram study a bit because I think that has important information about how you as investigators interact with your staff.

The study of untreated syphilis in black males or the Tuskegee Study was a study done with the purpose of identifying the natural history of untreated syphilis. And you might say boy that seems really bad. Take somebody with syphilis and not treat them.

But in 1932 when this study was first started, there were no effective treatments for syphilis. The effective treatments basically or the treatments were essentially arsenic and bismuth injections and it was very unclear whether the neurologic complications that people were having were related to being injected with arsenic or whether they were being related to having syphilis for long term. So they proposed a study to help decide what is the background incidence of neurological problems and other problems in men who have syphilis.

So they took three hundred black syphilitic males in 1932 and followed them for a period of time. In 1933, they expanded the study to add three hundred controls. And the study went on for ten years, even though initially it was just going to go on for about one year.

Now in 1943, ten years later, penicillin became available for the military and was discovered to be an effective treatment for syphilis. Now penicillin was in extremely short supply at that time. World War II was going on. And the military kept penicillin stocks for its own use to use with soldiers.

So what did the researchers do at Tuskegee? First they went to the Draft Board and they said you are not allowed to draft our subjects. Here's a list of subjects. They're off the list. The Draft Board said OK. Because they knew if they got drafted, their syphilis would get treated. The second thing they did is they went to the men in the study and they said you can't enlist in the military. Because they knew if they enlisted in the military, they'd get penicillin.

So they told them couldn't enlist. And they said if you do enlist, we're going to take away the economic benefit that we've promised you in this trial, which was that the men in the trial got to have a free burial, a proper burial. Now in this area, most of the men could never afford a free burial and they would end up getting some sort of pauper's burial. And for them, the free burial was something they couldn't afford, but was something socially very important to them.

In 1949, the Nuremberg Code came out. Nobody made any connection between the Nuremberg Code and Tuskegee. And in 1951, penicillin became widely available to the public. And at this time, it was clear that it was an effective treatment for syphilis. What did the researchers say? They said boy this study has been going on for nineteen years. If we treat these men now, we're going to lose this once in a lifetime opportunity to continue to follow and see what happens over time.

In 1966, thirty-four years after the study was started, the Public Health Service Policy comes out and says you have to have local Ethics Committee review. There is review and again they say well this is a once in a lifetime opportunity. We're never going to be able to take a group of men
with syphilis and not treat them again. So let's avail ourselves of this opportunity. And the study was approved.

Well, in the end, twenty-eight men died of syphilis. There were a hundred cases of disability caused by the syphilis. There were nineteen cases of congenital syphilis. So there were a lot of harms that came out of this study.

Now, this study has certainly some problems as we look at the Belmont Principles. There's a problem here with respect for persons. There was no informed consent that was done. In fact, there was deception. The men were told that they were getting treatment when they did spinal taps when in fact the spinal taps were done purely for research reasons. And there was coercion because an economic benefit that was dangled out in front of the men and they were told if they leave, they lose that benefit.

In addition, there were problems of beneficence because there was a withholding of effective treatment and there was no continuing review of the research. Because what might have potentially been ethical if you had informed consent in 1932 clearly became unethical over time in terms of the issue of beneficence alone. In addition, there was an issue of justice. We have an extremely vulnerable population, illiterate, poor, farmers in rural Alabama.

In response to this, Congress started a Syphilis Ad Hoc Study Panel which quickly reviewed the Tuskegee Study and said this study has to be stopped immediately. Their other observation was that there was inadequate oversight of human research. And they recommended that there ought to federal regulation of human research.

In response to that, the National Research Act was passed after a series of hearings by Senator Edward Kennedy in an initial attempt to have all research conducted in the United States governed by federal regulations. But the best that could be done was to say that research funded by the United States would follow the regulations.

And in May of 1974, 45 CFR 46 in its first version was published. The National Commission was formed in June of 1974. And in April of ’79, the Belmont Report was written. And again, I think the Belmont Report is required reading for everybody involved in research. Very short document, several pages long, but very, very clear elucidating information about the importance of the underlying principles governing research.

And in 1981, based on the recommendations pretty much that came out of the Belmont Commission, we have the regulations that we pretty much have today, which is the revised 45 CFR 46.

**Applying Research Ethics – 5:54**

In this module, I want to talk about now then how do we apply research ethics and the regulations. And we have really three protections from our federal regulations. We have the concept that we have to have prior IRB review, prior review by an independent board not
involved in the research. That we have to have informed consent of subjects in the research. And that we have to have institutional assurances.

Now, assurances are the fact that when you get money from the federal government, like through NIH funding, your institution signs a document called Assurances with the federal government. And it says that you will abide by the Belmont Principles and you will abide by the federal regulations in the conduct of your research. And most of these assurances also say that not only does that apply to federally funded research, but it applies to all research done by your institution, regardless of the source of funding.

So what makes research ethical? If you look at the three principles from beneficence, I think we can have the idea that we should have social or scientific value to the research, scientific validity to the research and a favorable risk/benefit ratio. From the idea of justice, we have the ideas that we should have fair subject selection, that we should have appropriate inclusion and exclusion criteria for the research and that we should have appropriate recruitment. Because certainly you can have a protocol that on paper has appropriate inclusion and exclusion criteria and fair subject selection, but due to the way that recruitment is done, you might have defacto, an unjust situation where you're targeting particular populations.

From respect for persons, we have a concept that we should have initial and continuing review of research and we should have allow people to withdraw from research and that we should maintain the welfare of subjects. And I think the thing that holds this together, the glue if you will, is really the prior independent review by the IRB, to put these things together and help you be sure that those are present.

So I want to go over each of the principles and have you think about when you're designing protocols, what sort of questions should be asking yourselves in applying these principles to your research? From the idea of beneficence, I think you should ask questions like can the research design be improved? Because better research is better for the subjects. It is kinder to the subjects. What are the risks? When you do research, look at your protocol and try to enumerate all of the possible risks that you have in that research. And then think about those and say what can you say what can you put into the protocol to help minimize those risks? How can you have additional monitoring? How can you design the protocol in a way that the likelihood of those risks are minimized or the intensity of those risks would be minimized?

What are the benefits involved in the research? And enumerate them and then think how can you design this research in order to maximize those benefits for those subjects? From respect for persons, I think it's good to ask questions about how you in your consent process can maximize autonomy. Are there a series of people who could discuss with a patient the process of what they're going through in the research? Have a coordinator or nurse sit down with them, then having the investigator sit down. What's the process that you can have to convey the information effectively to the subjects, answer their questions so that they can make a good decision?

Can you include things in your consent like allowing people to take the consent home, discuss it with their family, discuss it with their referring physician, their primary care physician. Are there
things that you can add that will help maximize the autonomy of your subjects?

How can your protocol maximize autonomy? Can you put things into your protocol in which at various times the subjects will be re-explained particular issues that are going to be coming up, their questions answered and for you to continue to be assured that they have their personal willingness to continue in that research?

And what additional protections can you put in if you have children or people who have limited ability to make decisions for themselves, vulnerable populations? What can you do to help protect them from the fact that they have a limited ability to make their own decisions?

And another issue is how can you design your study to maximally protect subject privacy? One thing I see in a lot of research is a collection of a lot of information like medical record numbers and social security numbers and other issues that you could probably delete from a lot of research and it would not affect the quality of the research. So if you have private information that you're collecting that you don't need to collect, I would say cut it out.

Now sometimes you need to collect social security numbers because you might need to query, for example, the National Death Index and then you need that information. And that's fine, but I think it's important to look and make sure. Look at all of the information you're collecting and say what is it that we're collecting that we have to have? Collect that and not collect the additional information.

In addition, I think it's important to look at the processes that you have for the ways that people can get access to the identifying information. Are there a limited number of people who have access to that information? And when you send samples out for testing to other labs, is it sent say with a coded ID number instead of with a subject's name, social security number and telephone number on it? So there are ways that you can design into your protocol to help maximize subject privacy.

From justice, asking the question of how can you ensure that recruitment will not unfairly target a particular population or will target the population that will benefit from the research? And how can you be sure that the research will not unfairly target a population? Again, if you're conducting research and what you decide to do is to conduct recruitment in such a way that the only people who you recruit somehow are people who don't have insurance or are people from the inner city of your town, then I think you have to ask the question what are you doing in recruitment that doing that. And how can you modify recruitment to help expand the population so that certain groups are not taking the burdens or other groups are not getting the benefits.

And I think it actually goes the other. We certainly see research where the only people who can participate in the research are those that have insurance or those that are wealthy enough to afford the drugs or devices that they have to pay for in order to be on the research. And I think that's another unfair aspect when that occurs in research.

How can you make the inclusion/exclusion criteria fair? Sometimes there are inclusion/exclusion criteria that don't make sense. And we certainly have seen that. Years ago, we don't see it as
much, where they say women cannot be involved in this trial because we don't trust women to not get pregnant is usually the excuse. Saying that people over a certain age cannot participate. Is that done on a rational basis or is that done in a way that makes it unfair for people who happen to be women or happen to be older? Those are issues to think about in designing your protocols.

Key Issues in Research Ethics – 30:43

I'd like to next talk about some key issues in research. These are questions that come up a lot and I want to go over these specific issues to help you understand some important concepts in research ethics. And they are understanding the term risk, understanding the term benefit, knowing when it's ethical to conduct placebo control trials and looking at your relationship as investigators with your staff and also your relationship as an investigator with your subjects.

Let's go over risk. The definition of risk is that it is a probability of harm occurring as a result of participation in research. And when we evaluate risk, we can quantitate those risks according to the probability or the likelihood that they will occur. And the magnitude of those risks. Is the risk something that occurs one in a million or is it something like vomiting after chemotherapy or hair loss after chemotherapy, which occurs in virtually 100% of people? Is it something that has a mild magnitude? It's one day of itching. Or is it something that's severe like an anaphylactic reaction that may lead to death?

And we need to think about the different types of risk. In medicine, investigators tend to focus on the physical risks. You think of the adverse events of the drugs or the devices. But I think it's important to think about social risk, legal risk, economic risk and psychological risk.

There are social risks because sometimes when people are involved in research, the very fact that they're involved in research that might involve people with sexually transmitted diseases or they're involved in research that looks at criminal behavior or research that looks at people with AIDS, that that can have a social stigma, just by their participation in that research.

Research can also have legal ramifications. If you collect data about illegal criminal behavior and that becomes public, that can put those people in your research at legal risk.

And there's also economic risk. I certainly see this in some drug and device studies, especially device studies where people are charged for the device and they may not realize that this is a $40,000.00 device that their insurance company may not pay for. And then they get stuck with the bill. That's a major risk.

And there are also psychological risks in research and I'll go over a study that is completely non-medical, but had tremendous psychological risk.

And the risk may also apply to individuals or they may apply to society or groups of individuals. If I do a survey of physicians at your medical center and discover that 38% of you have drug or alcohol abuse problems and I publish a paper saying hey 38% of the people, the physicians at
this medical center have drug or alcohol abuse problems, that's going to put everybody at risk in this institution, whether or not you participated in that research or whether or not you as an individual happen to be one of those 38%.

What is benefit? Well, the definition of a benefit is a valued or desired outcome or an advantage. But there's a problem with this definition and that is that when we do research, one we can't promise benefits. We say that in all the informed consents. We can't promise any benefit to you. You might have these benefits, but we don't know. So what I urge people to do and I urge you to look at is instead of thinking of benefits as just something good happening, think of it as the probability of a benefit happening as a participation in research. So when you're doing risk and benefit analysis, you're looking at the probability of something bad happening versus the probability of something good happening. And that kind of gets the risk/benefit equation into equal units, if you will.

And it's important when you're looking at a risk/benefit analysis that in your mind although payment for participation is certainly a good outcome for people that might occur as part of a study, it is not something that you can put into the risk/benefit analysis. So you cannot balance that risk/benefit equation by lumping money on the benefits side. That doesn't count.

And when you evaluate benefits, you can do this a lot, like risks. You can think about them in terms of their likelihood and their magnitude. You can think about the different kinds of benefits, medical or psychosocial or kinship benefits. Sometimes people get benefit by the fact that they are helping their family, they are helping other people with similar diseases. And again, the benefits may apply to individuals or they may apply to society, the importance of the knowledge that we might have gaining out of that research.

Another question that seems to come up a lot are issues of when is a placebo controlled trial ethical. And I urge you as investigators to think about these issues as well because this is something that's becoming a more important topic over time.

I think there are three situations in which you can consider a placebo controlled trial ethical and I'll go over each one of those. The first one is a situation where the outcomes of placebo do not include death or disability. For example, if you are doing a study of allergic rhinitis in adults, what is the outcome of taking those people and putting them on placebo for six weeks? They have a runny nose. It's not something that's going to subject them to death or disability. They're going to feel uncomfortable for six weeks. And the idea I think is that adults can make that decision that they don't mind being uncomfortable for six weeks in the name of science and that should be fine.

Another issue is when that there's a failsafe rescue from all bad outcomes. A good example of this are a lot of asthma studies where there is an active drug compared against placebo, but all subjects in the trial get an inhaler. And they are told that if they start to wheeze, they are to use that inhaler and call their doctor. And that inhaler acts as the failsafe rescue medication that makes sure that anybody, either an active drug or a placebo, will not suffer death or disability in that particular trial.
You can also do this with close monitoring. If you have a situation where people can call you early enough where they begin to feel some sort of effects that might lead to death or disability and they can call you early enough so that you can immediately take intervention or do evaluation to prevent death or disability, then I think that's something that can make a placebo controlled trial ethical.

And the third issue or most complicated issue is that when there is clinical equipoise and the research is designed in such a way as to disturb that clinical equipoise. And I want to go on and then I'll explain this term, clinical equipoise.

Clinical equipoise means that there's a genuine uncertainty on the part of the scientific expert community about the relative merits of the active arm of the trial and the placebo arm of the trial. Now, when you say that there's clinical equipoise, a lot of people say oh does that mean that every doctor has to say that they don't know which arm is better? And the answer is no. In fact, I've never seen a trial that has two arms in which you can ask a physician which arm do you think is better and they don't have an opinion. I mean everybody, because physicians are always in that situation. You can't go to your patient and say we're just going to do both arms because they're equal. You have to pick A or you have to pick B. And so physicians are used to the idea of taking all of the evidence and making some decision. I think one is better than the other.

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And you'll find that clinicians will disagree, but it's usually a respectful disagreement. It's a situation where they might say, "Well, I wouldn't say that's wrong. That is what my partner does. It's not what I would do for my patients, but I can't say that it's a wrong thing to do." And I think when you hear physicians discussing various treatments that way, then you know that you're probably in a situation where you have clinical equipoise.

And I think another issue is to combine the concept of placebo with the idea of respect for persons. And that is that when you have a placebo controlled trial whose execution is basically predicated on the fact that there is clinical equipoise, then you want to think about the concept of maybe only including subjects in that trial who also have a similar equipoise.

It's not an easy thing to do, but it's something to think about because sometimes certainly when you have non-blinded studies, you have situations in which subjects go into the study and they kind of know that they want arm A, they do not want arm B. And when they get randomized to arm B, they go "uh oh, I'm outta here." Or they get very upset and they demand arm B, even though arm B might be an experimental arm that is only available in the context of the research trial.

So I think you'd want to careful about those situations and think about the fact that patients can have clinical equipoise also and may have strong feelings about which of two particular arms might be more appropriate for them. And this idea I owe to Robert Veach.

I want to go over now about your relationship with your staff. This comes out of my unfortunate experience as an IRB Chair of having to conduct noncompliance investigations. It's the worst thing about being an IRB Chair, I think. Most depressing thing. And one of the most depressing things when I'm doing this depressing thing is when we're sitting there taking interviews of people involved in the research. And we have a staff member who comes up and says, "oh yeah, you know, I told the investigator that I didn't really think that what they were doing was right. I wasn't sure, but I told them I felt uncomfortable with it." And the investigator essentially brushed them off and said, "No, I've looked into it. It's really OK. Don't worry about it. I'll take all the responsibility." And they do.

To kind of go over this, I'm going to give you an illustration of one of the research studies in my Hall of Shame that I had called the Milgram Study. And the purpose of this was to determine response to authority. Stanley Milgram was a behavioral psychologist. He read all of the transcripts of the Nuremberg Trials and the newspaper reports and was just greatly upset by the
fact that all these people committed these atrocious, outrageous acts. And what was their excuse? "I was just following orders. I was doing what somebody told me to do." How could people do that?

So he decided to design a study to look at this. And so he recruited volunteers ostensibly to help study learning and memory. And what he did was he took the subject and he said, "You are a teacher. Behind this glass booth over here, I have a student. And you're to teach that student. Now when you teach that student and they make errors, we're going to reinforce learning by punishing errors with an electric shock."

And there was a meter that they had. And the meter had voltage on it dialed up from like one hundred volts up to three hundred and fifty volts, including a section on the meter that was big and red, with the markings on it that said "lethal" if you're in this range. So the teacher had to punish the student with electric shocks when they made errors.

Now, unbeknownst to the subject (who again is the teacher) is that the student was really a confederate of Stanley Milgram, another graduate student who was actually not getting electric shocks but was told to fake being a bad learner. And when that button was pushed, a little light went off. And at that point, the student had to fake getting an electric shock and scream and cry and make it proportional to the amount of voltage that they were getting. Plead for mercy and at times, they faked unconsciousness.

And Stanley Milgram would be behind them saying, "This person has missed a certain number of questions. It's time to give an electric shock. And it looks like two hundred volts isn't working. So the protocol says we've got to go up to three-hundred." And then to four hundred and so on. So he pushed the voltage up each time people made mistakes. And people got higher and higher voltages.

Well, it turns out that 63% of the subjects Stanley Milgram was able to coax to give the students lethal level of shocks. And even 65%, he was able to get people to administer shocks, even when that student said, "I have heart disease and if you keep giving me these shocks, I'm going to die."

Well, the Milgram Study had some ethical problems with it which I feel compelled to go into. And certainly there's a problem for respect for persons. This is a classic study about deception. Not telling everybody everything about the research. Not getting true informed consent. In a sense, lying to people about part of the research.

And there's clearly an issue of beneficence. This is a study that is a classic for psychological harm. Stanley Milgram writes in his book, "I observed a mature and initially poised businessman enter the laboratory, smiling and confident. And within twenty minutes, he was reduced to a twitching, stuttering wreck who was rapidly approaching a point of nervous collapse." This study had no drugs in it. This study had no medical interventions. But you have severe harm, much more severe harm than I think we find in a lot of medical studies that we do.

So the lessons from this I think that I want you to learn is that people can readily perform unethical acts in the presence of an authority figure. Now, authority figure doesn't mean
authoritarian. Doesn't mean somebody's going around barking orders to people and saying, "you
do this or else." Authority usually means somebody who has the answers. Somebody who
people respect. Somebody who's in a position of respect like principal investigators.

If you're a principal investigator, hopefully most of your staff looks up to you. They go to you
because you have the information that your staff needs. You are the leader. You're the guider.
You're the person who knows. And I think it's important to understand that these authority
relationships not only occur between you as principal investigators and your staff, but they're
also there to some degree between you and your subjects.

Also, with the sponsor over you. You have to be careful. The sponsor may say, "It's OK. Go
ahead and do this. We checked with the FDA and they said it was OK." And so you think well it
doesn't seem right, but I'll go ahead and do it. And remember, your tendency will be to follow
what the person in authority tells you to do. That's the lesson of the Milgram studies.

It can also occur with the protocol over as an authority over you. And if you think about it, what
was Stanley Milgram doing with his subjects? He was saying, "Well, the protocol says that
when you miss three questions, you go from two-hundred volts to two-hundred and fifty volts.
That's what the protocol says. This is science. That's what you have to do." And people were
responding to his authority and the authority of the fact that there was a scientific protocol.

You can still get Stanley Milgram's book on the internet and it's kind of interesting because if
you go to the Web and you do a search for Stanley Milgram, you will hit about one thousand
militia web sites. Why is that? Because militia web sites think it's really cool, this idea that you
should distrust governmental authority and not have obedience to the government.

But I think the response of this that we should have is to learn what the airline industry calls
crew resource management. In about 1985, there were a lot, we were having a lot of commercial
airline accidents. And the FAA would investigate these accidents and they would find that if you
listen to the cockpit voice recorder, there would be situations where the pilot was warned by the
copilot or engineer about the particular problem. And the pilot brushed them off.

Or situations where they knew that the engineer was looking at an altimeter that said that they
were two hundred feet from crashing and they didn't say anything to the pilot, because they
figured well the pilot must be flying at two hundred feet because they're the pilot. They know
what they're doing.

And it was this situation where the pilot had this halo effect. The pilot was God in the cockpit.
Could not do anything wrong. And people were either afraid to tell the pilot or they would tell
the pilot and the pilot, because they were such an authority figure, would tend to brush off what
other people would say.

And what I have seen is that the same thing occurs in research between coordinators and staff
and principal investigators. So I think it's important that you as investigators need to encourage
your staff to ask questions. Whenever they're uncomfortable about something that's going on,
they need to bring it to your attention.
And when they bring it to your attention, then you need to listen. And you need to understand that it's very easy. I've been there before myself. It's very easy to sort of listen. "Oh, it's OK. Don't worry about it." You really have to listen, understand what's going on and take it very seriously. And think this person might be telling me something that's going to keep me out of hot water.

And I think it's important to build consensus. Make sure everybody in the group feels comfortable with what is being done with the processes and procedures. And if you're not, go ask somebody else. We do this in my IRB. When we look at procedures, anybody in the office - staff member, secretary, manager, looks at a procedure and says, "I'm not really sure that this is right," we go ask somebody else. We go to the Feds and we say what do you think? Do you think this is right or not?

And it's important also to eliminate intimidation. You really want people to feel comfortable to come to you and to ask you questions. And if you're the kind of person that says, "don't bother me, go do it yourself, figure it out yourself," you're going to end up in situations where I've seen investigators where the person was trying to tell them about somebody who was forging data or there was a problem where somebody was not following procedures. And the investigator said, "I don't want to hear about it. I want you to solve the problem." And the investigator never heard about it even though they were told about it. And that ended up later in a big problem for the investigator.

Let's go on and talk about investigator/subject relationships. I think it's very important, in fact I think it's fundamental to research that the investigator is really the person who has to place the subject's rights and welfare and safety above all other personal and scientific concerns. And this is a moral fiduciary relationship between you as an investigator and your subject.

Well, what does that mean? Moral fiduciary relationship. It means that protecting the research subject is your primary concern. It also means that your self interest has to be blunted by the obligation to protect the subject. And your self interests include for example the fact that you want to recruit subjects for the research and get the data, a very legitimate interest on the part of investigators. But it is important that that has to be your secondary interest.

Again to take the pilot analogy (I love the pilot analogies), that when you fly in an airplane, you know that that pilot's job is to get that airplane from say Albany to Pittsburgh, like the pilot was last night. But your hope is that the number one concern of that pilot (and I think it is the case now) that that pilot's concern is your safety. And if the plane can't land in Pittsburgh and instead has to land in Philadelphia, I'm upset. You guys are upset because I wouldn't be here. But that's the way it goes. My safety is first.

And I think it's really the same way in conducting research. Your job, in part, is to get the patient through, get the subject through the protocol. But the number one issue is the protection of that subject while they're in that protocol.

And in the end, you have to think of scientific knowledge, the remuneration from that research,
the prestige from the research as really being side effects of this relationship that you have with your subject of being there to protect them in their travels through that research.

The moral of fiduciary relationship is similar to the physician/patient relationship, but I think in some ways, it's different. For example, with informed consent, as physicians I think we're used to having more weight placed on the principle of beneficence relative to the principle of informed consent in emergency situations or in situations in which patients come to us and they say, "Doc, yeah I've heard these issues. I don't really want to make a decision, but I want to do whatever you think is best." And they delegate their autonomy to you. I think something like that is much more acceptable in medicine. It is not acceptable in research.

In addition, there's the issue of withdrawal from procedures. We are used to in medicine where we have a defined benefit of really going to whatever ends we need in order to complete procedures. And in research, you have to be much quicker to withdraw people from researcher because you are there really to protect them from the research. It is not something they necessarily have to be participating in.

Another important issue with the moral fiduciary relationship is that it allows you to deal with conflict of interests. This is something that's coming up a lot. My concern with conflict of interests and the current interest in this is that people want to stamp out conflict of interests. And my response is that you can't stamp out conflict of interests unless we have all investigators take vows of poverty and chastity and obedience. I like the idea of obedience. I think that would be a good vow.

But clearly, we're not going to have investigators give up everything in their life so that their whole purpose is focused on the subject. People have different interests in life. Investigators want promotions. They're under pressure from their institutions to bring in more research dollars. That's fine. As long as investigators understand that their primary interest in conducting research is to protect the subjects and that the other issues are secondary.

I think it also allows researchers to be their subject's physician, as long as they understand the difference between the relationship to a patient and the relationship to a research subject. And it is the basis of societal trust in researchers. It's like the basis of societal trust in getting on that airplane. If you thought that the pilot's sole concern was to make a lot of money and be there on time, you'd have second thoughts about getting on that airplane.

And when subjects allow themselves to be participants in your research, I think they do it out of a lot of trust. I'm sure everybody can recognize this. They do it out of a lot of trust because they believe that you wouldn't be doing this to them if you were putting them at excessive harm. It's important to remember that trust and when people are in situations where they may be leading to excessive harm, to withdraw them from the research. And so this is just essential.

I have friends who do research with African Americans, looking at racial variation among coronary artery disease. Very, very difficult to recruit African Americans because African Americans look at Tuskegee and they say, "We lost the trust. You guys abused us. I'm not going to allow myself to be a guinea pig like those men were." And so in this situation, it's the same
thing that if we do not maintain this relationship and maintain this trust, we're not going to have subjects and the whole game's going to be over.

I want to go over a particular event that occurred, a death of a normal volunteer, at the University of Rochester in March of 1996. I had the opportunity to work on a New York State commission that looked into this death and issues that needed to be considered in the conduct of research.

This was a nineteen year old Asian American student who responded to an ad for bronchoscopy in order to harvest alveolar macrophages. Now, she had a very difficult time with bronchoscopy and she required numerous doses of lidocaine. And I don't know if any of you have seen bronchoscopy or done it, but it's a lot like a lot of other medical procedures. It's not comfortable.

On the other hand, most people by giving them topical lidocaine, by talking them through it, explaining the procedure, having them breathe, you can usually get people through bronchoscopies comfortably. Maybe not comfortably, but not that they would ever do it again. But they get through it.

Then you have some people, they're like these guys that are on Friday night on Fox television that are sticking things down their throat and stuff and they seem to have no gag reflex. And you do have people who are able to do bronchoscopy with almost no anesthesia. That was one of the people to me actually used to bronchoscope himself to show people how easy it was. He was an unusual person.

You also have unusual people on the other end who no matter how much talking or topical lidocaine you give them, their gag reflex is so great that they just can't get through the bronchoscopy. And those are people usually end doing under conscious sedation or general anesthesia in order to get the bronchoscopy done.

As I read the record, this woman was in that group of people who had an extreme gag reflex and just had an extremely difficult time. And the investigators kept giving her lidocaine. Now, the investigators understood. They said, "Well, boy you're having a hard time with this. Do you mind if we go ahead or do you want us to stop?"

And she shook her head "yes" that she wanted to continue. There were some issues because of the fact that she was Asian and what shaking her head means, but the investigators, for the sake of argument, we'll say that she asked her and that she indicated her willingness to continue with the study. She however returned in cardiac arrest with a lidocaine overdose and died a couple days later after a successful completion of the bronchoscopy. And she had a tremendously high dose of lidocaine.

Now there was an investigation into this. Of course, OPR swarmed in and the FDA swarmed in and New York State came in. And everybody did their investigation. And they said, "hey guys, you didn't limit the dose of lidocaine." And that was a problem. They noticed that the lidocaine dose wasn't documented, that the patient wasn't observed after bronchoscopy. That the lidocaine concentrations were increased in the protocol without prior IRB review.
Now some of these were problems but I'd look at this and I wonder whether any of this really would have been detected prospectively or whether if they did indicate to the IRB that they were going to go from 1% lidocaine to 2% lidocaine that anybody on the IRB would have said anything about it. And in fact, this is actually really a sentinel case. This is the time that people learned that you could die as a normal person from a bronchoscopy. And before then, people would pretty much say nobody's really died of a bronchoscopy if they are normal.

So it's hard to say whether any other IRB would have picked this up. And as I look at it, I think if it came through our IRB, we would have approved the protocol. We wouldn't have necessarily required documentation or limitation of dosing of lidocaine. In 1996 we would have done the same thing. There have been guidelines published since then to indicate that you should do these things, but that was after the fact.

What I really see as the major problem of this, the thing that I found disturbing as I read the case history is the idea that I think that these investigators breached their moral fiduciary relationship with this subject. These investigators should have withdrawn the subject. They should have said, "You are having a very hard time and we know that we can go out there and we can get people who don't have anywhere near as hard a time as you have. But you are suffering a lot."

And really not on the basis of the medical risk of the lidocaine, but literally on the basis of the suffering that this woman was going through from this extensive, prolonged procedure that wasn't going well, to just be able to say, "I know you want to continue and we appreciate that. But here's the money that we promised you for participation in the research. You've been a great subject. And we're glad you participated and we're very thankful that you were here to help us." That's it. We're going to end it right here. And that would have saved this person's life.

So the lessons I think are that acceptable risk for a patient where you might in a patient, you might consider going on and on and on in order to get the bronchoscopy done would not be an acceptable risk for a subject. And also here that informed consent does not equalize the subject's knowledge with your knowledge as an investigator.

So investigators, if you're an investigator who's doing a bronchoscopy, you've hopefully done a couple hundred bronchoscopies and you know that there are people who have a really easy time and people who have a really hard time and a big group in the middle. You can tell the difference between them. The subjects can't. The subjects experience one bronchoscopy. And what did they read in the informed consent? "We're going to do the bronchoscopy and you're going to cough and gag and feel miserable for awhile."

Well, that was what was happening to this subject, but she didn't realize what the investigator knew and that was that she was way off the curve in terms of the amount of suffering that she was experiencing.

So I think it's important that you as investigators use your knowledge in order to protect subjects and that you should withdraw subjects from trials who are not tolerating the procedures. And I think that can be as true for a simple venipuncture study. That if you're in the lab commonly, like when I was in the lab, we used to go around drawing blood on each other so we could isolate
leukocytes and fibrinogen. You have people in the lab who have good veins and you have people in the lab who have bad veins. And you might have a situation where you have somebody with bad veins and you stick them a couple times and you can't get the blood.

And that person says, "Oh, I don't mind. Get somebody else. Have them draw the blood." And they try a couple times and they can't get the blood. And they say, "Oh I don't mind. Try my ankle. I don't mind. I want to get the research done."

Well, I think it's appropriate to say that as the investigator, if you were supervising that to say, "No, we're going to find somebody with good veins because what we're doing is we're subjecting you to more discomfort when there's no benefit to you. Let's go find the people with good veins. We'll get the blood from them."

So withdrawing people like that even from a research study. And I want to thank you very much for your time. And that concludes the end of our presentation here.