

## ***Testing New Drugs: Are People Guinea Pigs?***

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**ROBERT TEMPLE:** You cannot deny people a therapy that's available to them, um, if harm will come to them.

**ANDREA KOVACS:** Our children were dying and now, and our adults, through clinical trials we've been able to determine the optimal therapies and we really haven't had anybody die in our clinic, at least of children, three or four years.

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**ALEXANDER CAPRON:** One thing we have to recognize in this country, is that a lot of people sign up for clinical trials because it's the only way they can get effective treatment of any kind. People who go to trials that are now often run through private doctor's offices, on contract to drug companies and so forth, because they don't have the money to go into that doctor's office and get care that they're going to pay for, but the doctor, but there's an ad they see in the paper, "if you have xyz disease, come in, we'll treat you," and what you're doing is signing up as a guinea pig in a trial.

**ROBERT TEMPLE:** We have clinical control trials largely because Congress, in its unbelievable wisdom, in 1962, said control trials are the only basis for proving a drug. So the drug industry, which is a very bottom line group of creatures, said, okay. And maybe ten years later, everything's a clinical trial.

**ROBERT L. KUHN:** What is compassionate use?

**ROBERT TEMPLE:** Compassionate use refers to use of a drug specifically directed at treatment of an individual person, not to learn something.

**ALEXANDER CAPRON:** But this is a drug that isn't yet approved for that use.

**ROBERT TEMPLE:** It's usually referred to, very early use of drugs that really aren't fully developed yet, for individuals who appear to have exhausted available therapy. The trouble with it is, used that way, you often know very little about the drug and you can be surprised by the toxicity, too.

**ANDREA KOVACS:** You could have the wrong dose, and with a disease like HIV, the wrong dose could be disastrous.

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**ROBERT TEMPLE:** We had a advisory committee meeting on this very matter related to cancer drugs, and many members of the patient advocacy community came to sound a note of caution, they said it's not always a favor to people to use an untested drug in a lot of people, and I was very impressed by the capacity they brought to the whole discussion, it was very good.

**ROBERT L. KUHN:** Andrea, tell us about your work on AIDS, and the issues that you have regarding clinical trials.

**ANDREA KOVACS:** I'm the director of Maternal, Child, and Adolescent Program at USC, and we follow at the present time, over 600 women, children, and adolescents, and about 20 or 30 pregnant women at any one time. Over the last 10 years, we've seen tremendous progress in terms of successes, for instance, when I started about a third of the babies born infected women were infected, now there're zero. We can actually prevent transmission again, this was a result of clinical trials. Our children were dying and now, and our adults, through clinical trials we've been actually able to determine the optimal therapies and we really haven't had anybody die in our clinic, at least of children, in three or four years, so we've had tremendous successes, I think without clinical trials we wouldn't have had these successes.

**ROBERT L. KUHN:** So what are the issues you're wrestling with now?

**ANDREA KOVACS:** How to enroll someone between the age of 7 and 13, who basically doesn't know their diagnosis, whose parents want them in clinical trials who can't get them through compassionate use. How do you enroll such a child, who has to sign a written assent that has the HIV diagnosis in the assent.

**ROBERT L. KUHN:** And the child doesn't know he or she has HIV.

**ANDREA KOVACS:** And the child doesn't know HIV. We've had families get thrown out of their neighborhoods, kids get punched in the face because their diagnosis was disclosed. So, it's very complicated because disclosure is such a huge issue with the disease, with that kind of discrimination that there is.

**ROBERT L. KUHN:** What is the difference, if you between consent and assent?

**ALEXANDER CAPRON:** The assent was a recognition that, for people who are not yet of the age of consent, they're under 18 they ought not to be involved unless they agree, and that agreement just has the term "assent."

**ROBERT L. KUHN:** Is it realistic to ask a seven-year-old to give an assent to participate in a clinical trial?

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**ROBERT TEMPLE:** There's no absolute rules about this, people draw lines where they think they can, but I think seven is an age where people believe that the child can make a reasonable decision. Below that, it probably isn't.

**ALEXANDER CAPRON:** If my kid says, I don't want to have this or that procedure, and the doctor and I have concluded that this is the right thing, I will try to persuade the kid, be as comforting as I can, but in the end, I say, "This is the treatment we're going to do." But if I'm "volunteering my child," as opposed to volunteering myself, to be in research for the benefit of science and so forth, if I can't do that without some level of the kid saying, "I'm willing to play that role, because it's a role that isn't just for my own benefit."

**ROBERT TEMPLE:** This is the easiest ethical principle for me to understand, a person is supposed to volunteer and supposed to know what they're getting into. Well, it's not easy to convey to people the complexities of a study. You have to tell them what the alternatives are, you have to do your best to tell them what the risks are, you have to not over-promise on the benefits side, that wouldn't be fair either, and you have to not only give a written document, but you have to be available for questions, it has to be language appropriate, it's very hard to do that and...

**ALEXANDER CAPRON:** There's a real risk that people go into them thinking that they are going to get a benefit from participation, and the need to explain that what you are doing is research. You hear constantly from physicians in these situations, that they'll go through a process of describing randomization and this is a trial, and then they'll say, are you comfortable, and the person will say, yes I'll sign, and then they say to the doctor, "I, know you're going to give me, the treatment that's right for me," and that, the whole notion is, when there's such cognitive dissonance, you, you, you did, that this is the person who's your doctor and he's basically saying to you, I'm doing something and I don't know if I'm giving you an inert substance or this thing that we're studying, and you want to say, "But you must be doing it for my good because you're my doctor."

**ROBERT L. KUHN:** Andrea, how do you do that with your adolescents, especially people who have not the highest education?

**ANDREA KOVACS:** 13 to 18 year olds who get HIV are not your routine 13 to 18-year-old. Frequently they're on the streets, they're not legally emancipated, how do you enroll a 13 to 18-year-old pregnant adolescent, how do you enroll someone who's in and out of juvenile courts. These are very complicated issues, this is a big challenge.

**ALEXANDER CAPRON:** I assume that in this group, there's no question that they would all know...

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**ANDREA KOVACS:** Oh, yes of course, they all know their diagnosis, but, at this point, I can't enroll anybody in, without a parent.

**ROBERT L. KUHN:** Is that the rule, she can't enroll these people who desperately need to be in these trials without parental consent because you can't get parental consent?

**ROBERT TEMPLE:** There can be a legal guardian who can do that.

**ANDREA KOVACS:** But you have to go to court.

**ROBERT TEMPLE:** But you have to go find one.

**ANDREA KOVACS:** Right, and so once we start doing these huge studies, which are going to be Phase III studies at some point, how do we do this?

**ROBERT L. KUHN:** I think it may be helpful at this point is if we can go back and define the various phases and what we hope to learn in, in each one.

**ROBERT TEMPLE:** The simplest kind of trial is treatment one, is the drug you're interested in, treatment two is, say a placebo.

**ALEXANDER CAPRON:** The usual design of research involves what we call blinding and that is to say disguising both from the subject and from the investigator what the condition the subject is.

**ROBERT L. KUHN:** Single blind, if the patient know, and double blinded if the investigator doesn't know also.

**ROBERT TEMPLE:** Phase I trials are the first introduction of a drug into humans, that's been studied in animals, and now you give it to a small number of people, sometimes normal people, sometimes people with a disease, you generally push the dose up until someone gets nauseated or dizzy or something like that, and it gives you some idea of what doses will be tolerated. Phase II is the first control trial of the drug, usually in a fairly narrow, well described population, and you're looking to see whether the drug really does what you hope it to do, in an HIV trial, that might be a comparison of one regimen with another to compare the effects on the virus, on the number of viral particles per unit of blood. Phase III is more control trials to better define the dose, look at the drug in various severities of disease, look at both men and women, black and white, old and young, and to generally get much more exposure so you can define the rarer side effects. After all, in a couple of hundred people in Phase II, you won't find something that happens in one in 500, but once you get into Phase III, you might have several thousand people, and you have at least a chance of finding side effects that occur at the 1/1000 rate.

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**ALEXANDER CAPRON:** That's where you then get into the issues of using a placebo control versus, what they call the active control. If you're doing an acne medicine or a hair loss medicine or something, of course you would do a placebo control because you're going to get results that are more reliable more quickly, and the fact that someone is going without their treatment for a brief period of time is not going to raise major problems.

**ROBERT TEMPLE:** The basic rule is you cannot deny people a therapy that's available to them if harm will come to them. Harm usually meaning something irreversible, death is irreversible, having a stroke is irreversible, everyone agrees, in that sort of case, you can't do a placebo control trial anymore. Consider depression, there are a lot of new drugs for depression, everybody's very excited about them, they've made a big difference in therapy. But it's a fact, only about half of trials of depression with Prozac can distinguish drug from placebo. Now, if you know that, and you now do a trial comparing a new drug with Prozac and it doesn't see any difference, well, what have you learned? Maybe this was one of those trials that couldn't tell Prozac from placebo. And you can't tell, if you don't have a placebo. So, we ask for a placebo control trials. Now, some people are nervous about that. After all, depression's not a completely benign illness, maybe people commit suicide. Fortunately, in this case, there are several large assemblages of data, called meta-analyses, that have looked to see whether people in the placebo group are more likely to commit suicide, and in the studies that are done, which, which are short term studies, four to six weeks, they're not. So, we can comfortably say it's ethically okay to do placebo control trials in properly informed patients, and it's essential to have that or we'd be approving drugs that didn't work.

**ROBERT L. KUHN:** Do you agree with that, Alex?

**ALEXANDER CAPRON:** I don't agree or disagree, because I think that there are certain things that are left out of that description. What the type of depression is, what are the circumstances of the subjects, all become very important, both as to their own ability to consent and to the safeguards that you could build in. If you're dealing with a relatively mild depression, where the likelihood of suicide or other harm is very small, it's one thing you might say, in other cases, that the patients would have to be in circumstances both where their consent was very reliable and where they were going to be given protection of medical care, and then, if you get to something where, where a treatment that would be available is being withheld from those people, is not offered to them, whereas other people are getting it and it is effective, although maybe there's something better on the shelf, that might be coming along, I want to say, I'm bothered by the quality of the consent there.

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**ROBERT TEMPLE:** We don't disagree on that at all. Those are important issues. If we don't have a placebo control trial for a new antidepressant, we are not going to be able to know whether it works and we can't approve it. Now, there are alternatives. If it's better than the available antidepressants, you can show that it's better. That works.

**ALEXANDER CAPRON:** That's somehow called a superiority trial, as opposed to an equivalency trial, which has this ambiguity that Bob points out.

**ROBERT L. KUHN:** Because there's no placebo.

**ROBERT TEMPLE:** The trouble is, in the hundreds of trials that have been done comparing one antidepressant with another, they've never been superior. They're all more or less equally effective.

**ROBERT L. KUHN:** Let's look at the stakeholders in clinical trials who it matters to, obviously, there is the patient group who have the syndrome or the disease that we're talking about, is obviously the government but there's a, a big elephant in this room and that's the drug companies, they invest an enormous amount of money in creating these new drugs. How does that affect the whole process?

**ROBERT TEMPLE:** Well, the drug companies, they obviously have their own views on everything, but they come to us and come to experts in the community for advice about how to do their trials. There's a million important questions, which control group is only one of them, another is what the endpoint of the study should be. We approve drugs because they lower cholesterol, what we really want to know is whether they save lives. Well, after many years, we now have a whole bunch of cholesterol lowering drugs that save lives

**ALEXANDER CAPRON:** The bigger issue there is the so-called me-too drugs, where there really are effective treatments. And the next treatment coming along is not being offered because it's cheaper or even necessarily because it has remarkably fewer side effects, but because one drug company wants to have something on the market to compete with the others, and there really isn't a huge benefit to the consumer.

**ROBERT TEMPLE:** However, the desire to find the place for your particular product has been beneficial on some occasions, the most striking case is with what are called statins, lipid lowering drugs, where multiple companies have each carved out situations in which they could try to show that their drug had a survival effect, if you have one gigantic study that takes place in Scandinavia that shows that the drugs are good for people who have had a heart attack and whose cholesterol's over 260. Then someone else does one in Scotland that shows even if you didn't have a heart attack and your cholesterol's over 260, it helps. To some extent, competition there does what it's supposed to do.

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**ALEXANDER CAPRON:** It develops more information than we would have had if you just had the first study.

**ROBERT TEMPLE:** In, in this, in this case, unbelievably valuable information. Now, lipid-lowering drugs, many of them, are known to save your lives and there's general agreement they're used too infrequently. So, it's at least a neutral thing, it costs a lot of money to get everybody on these drugs because they're not cheap, but, it's not necessarily a bad thing for the community.

**ROBERT L. KUHN:** Why is there so much criticism in the press about clinical trials and what the government does?

**ALEXANDER CAPRON:** I think there have been some trials which went very badly.

**ROBERT L. KUHN:** What's an example.

**ALEXANDER CAPRON:** one example is what happened at the University of Pennsylvania with their attempt...

**ROBERT L. KUHN:** Gene therapy.

**ALEXANDER CAPRON:** Their gene therapy, investigators were looking to get a gene functioning in patients with a very a rare disease, which mostly strikes very young children. And one young man, who had just recently turned 18 was enrolled, perhaps because he didn't quite, actually at the time the trial began, meet the enrollment criteria, which had been thought out to minimize risk there are many different arguments that have been raised as to why this happened. He got very, rapidly very sick and died.

**ROBERT L. KUHN:** And his condition was not life-threatening.

**ALEXANDER CAPRON:** And his condition was not immediately life-threatening to him because he had the version of it that was not as severe. Now, there's an underlying debate, would it have been better to do this, research in people who were critically ill, namely the little babies, who couldn't, obviously give any agreements to participate, but where the risk is balanced by notion that they're already very sick and if this worked, it would be a great benefit to them, whereas he wasn't going to really benefit from it, he was doing it altruistically. The other issue there, is the extent to which the researchers and, indeed, the entire research enterprise was tied into an entrepreneurial interest that the researcher and the university which had invested in this, had in the development of that technique.

**ROBERT L. KUHN:** So, the university had a financial interest?

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**ALEXANDER CAPRON:** The university had a financial interest and the investigator was basically a principal owner of the company that was sponsoring the research and that would, if the research paid off, have been in the position to benefit financially.

**ROBERT TEMPLE:** Who supports most clinical trials? Drug companies, obviously, they're interested parties. It's not always clear what their interest is, I think they really want to find out whether a drug hurts people, because they don't want to market that drug, that's a disaster for them, so, they don't want to suppress bad news, I think, although motivation is complicated to figure out. The ordinary way trials are done is that a drug company, obviously an interested party, pays an independent investigator, the assumption is that person has no stake in the outcome to do the trial and do it in a high quality way and they monitor the trials to make sure everything's filled out and stuff like that. That's the usual model.

**ALEXANDER CAPRON:** I think it is just as likely that, if we looked in detail at research done anywhere, we could find problems and I think we are coming to the point in this country where we recognize we need a better system than we have now for knowing, on an ongoing basis, how well institutions that carry out research are doing, and we've just recently had, it was a recommendation of the National Bioethics Advisory Commission, on which I serve, and I think the government is getting prepared to indeed say that programs should be accredited, this would start off as a voluntary activity, but, what it would mean is that not just when a problem arises, but on a periodic basis, people familiar with the way research should be done, would be coming in and taking an in-depth look at the procedures, at the consent, at the review, and, particularly how good a job do the universities do of watching things after they started.

**ROBERT L. KUHN:** Let me bring up another issue of ethical concern, and that is when clinical trials are done in third world countries that could not or would not be done in the United States at a point. There's a whole series of sensitive cultural issues that come up.

**ALEXANDER CAPRON:** And one pole would be a company wanting to develop something for the U.S. market, but doesn't think it can do the trial because there's an existing treatment here that is already effective and established. And so they say, well, we could go to a country where no one gets any treatment and we could compare our new treatment to a placebo. And the incentive for people in the other country doing it could be either that they're confused about what they're getting themselves into, or that the officials in the country have been offered something or paid something and induced for some minor...

**ROBERT TEMPLE:** Though the other thing is they may be better off than they would have been otherwise.

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**ALEXANDER CAPRON:** Yes, of course, they may think that they'll be better off because of this treatment, of course, the research intervention is likely to be very time limited and the product being developed...

**ROBERT L. KUHN:** Is not for them anyway.

**ALEXANDER CAPRON:** Is not for them, and it couldn't be afforded. You want to say you shouldn't be allowed to do that, that's wrong, ethically it should be wrong, the FDA maybe shouldn't accept such data. At the other extreme is a country faced with a first world treatment for something that's much too expensive, they want to develop something, their own scientists working with the scientists perhaps from elsewhere, come up with an alternative, let's say cost a tenth or a hundredth as much, they know from the beginning, that it won't be as effective, but they have nothing to offer, and this new thing offers them .

**ANDREA KOVACS:** I was just going to bring up the example of perinatal transmission, which is probably what you're talking about in South Africa and Thailand where there was this huge uproar over the fact that we have a standard in the United States, AZT during pregnancy at delivery, and to the newborn for six weeks, well, that can't be done anywhere in sub-Saharan Africa and many parts of the world. Well, a trial was done where one dose of Nevirapine was given to the Mom, to the baby versus placebo.

**ROBERT TEMPLE:** Actually that was a low dose AZT.

**ANDREA KOVACS:** It was the low dose AZT, but the idea is the same, is that, here you're trying out something, there is a proven drug that can prevent transmission by two-thirds, you're at trial, you are testing, in another part of the world, a modified version that you know is going to be inferior, but you cannot give standard of care there like you can here.

**ROBERT L. KUHN:** From the first world standard of care because they can't afford it.

**ANDREA KOVACS:** They can't afford it, they can't do it, they don't have the system, they don't have...

**ROBERT TEMPLE:** What they said was that the...

**ANDREA KOVACS:** You need a whole infrastructure. You need follow up...

**ROBERT L. KUHN:** And so you're giving a lower standard of care, but it's the only one that could possibly work in that area.

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**ANDREA KOVACS:** Absolutely.

**ROBERT TEMPLE:** The basic rule is you cannot deny people a therapy that's available to them, in that sort of case, you can't do a placebo control trial anymore. What the critics said was that the only acceptable trial was to compare low-dose AZT with this sophisticated regimen called the O76 regimen and...

**ROBERT L. KUHN:** Which is very expensive and complicated...

**ROBERT TEMPLE:** And even if you could do it um, it wouldn't answer the question these countries needed to know, which was whether short course AZT was effective at all. It didn't have to be as good as O76, it could be half as good, but, if it worked at all you needed to know it.

**ALEXANDER CAPRON:** The presumption is you can't do that kind of a study, there really is no way of doing the study with the comparison to the first world, that the first world drug is and under any reasonable circumstances not going to become available, that the drug you're testing and talking about could, and really there is some commitment to making it available and, I think as an additional requirement, that you make some additional contribution to building up the scientific and ethical review capability of the country so you leave something behind, beyond just having used their population as subjects. If you don't have kind of a presumption that you have to overcome with these very substantial and concrete requirements, then you open to the door to things that really would be very bad.

**ROBERT L. KUHN:** Such as?

**ALEXANDER CAPRON:** Well, your me-too work or whatever on poor people who would sign up to do anything, between the therapeutic misconception and the desire for a little money, they would literally become guinea pigs. I don't think that it's something that most American companies would want to do, but the temptation is certainly there. And you really ought to get review both in the country, substantial scientific and ethical review there and in the host country.

**ANDREA KOVACS:** Well the best is if it's done as a team effort.

**ROBERT TEMPLE:** It is a fact that many, many drug companies are now carrying out trials, just like the trials they do in the U.S., but additional ones, in Eastern Europe and in South America, for antidepressants, antihistamines, whatever it is. They may want to market those drugs sometime in those countries, but they're not going to do it anytime soon because the countries would use a generic version of the same drug, they wouldn't spend the money on the original. But, of course, these are all trials in which we believe the consequence of non-treatment is not to harm you.

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**ROBERT L. KUHN:** Well, you're using poorer people as your guinea pigs.

**ROBERT TEMPLE:** Well you're using your U.S. people in the same way as guinea pigs. I mean, antidepressant trials are done in Western Europe, in Eastern Europe, in Latin America.

**ROBERT L. KUHN:** Yeah, but if they're used here, at least if something works the peep, this population would be able to take advantage of it and the other population would not.

**ROBERT TEMPLE:** Perhaps true.

**ROBERT TEMPLE:** It is worth knowing, however, that as a consequence of doing trials in these parts of the world, they are leaving an infrastructure that is capable of doing trials, they may be leaving buildings behind, as well. They got access to diagnostic and other criteria and other steps they might not have gotten otherwise. Now, is that taking advantage or is that providing something good for them.

**ROBERT L. KUHN:** Truth is, it's both.

**ALEXANDER CAPRON:** You can argue both things, but the fact is they didn't have that before and they got it, is that an undue inducement or is it just...

**ANDREA KOVACS:** But, also, it could elevate the society locally and I think that's very important, if you can do that.

**ROBERT TEMPLE:** Well, I do too, I think they're trained in that, they can use the same skills...

**ANDREA KOVACS:** As long as you don't just go in and leave.

**ALEXANDER CAPRON:** Actually, that is certainly the worst thing.

**ANDREA KOVACS:** You train the people, you, you train the local groups, you bring in resources, and then you teach them how to do the studies.

**ALEXANDER CAPRON:** But, you know, sometimes the people that you're training and are benefiting are already the elite in the country, they are the scientists and the physicians and the people who are going to have access to the fancy equipment you leave behind and the buildings and so forth. And, yes, you may help indirectly the population by making them better off, but their agreement to participate and so forth is not necessarily equivalent benefit to the community. There are things you can do beneficially to the community.

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**ANDREA KOVACS:** Although I think HIV's an example that's helped, now we're going to start studying other facets of disease other than just HIV, TB, malaria, and so, here we're going to have such an incredible, positive impact on a society because of a terrible disease, but we're going to study the water, we're going to, you know, all these other benefits are going to tie in.

**ROBERT TEMPLE:** And people have complained probably with justice, that commercial and other interests haven't been as eager to study those things in the developing world as they should have be.

**ALEXANDER CAPRON:** Because they weren't diseases of our country.

**ROBERT TEMPLE:** Right, and because there weren't large amounts of money to be made from it. So, getting into those places actually strikes me, I mean, I believe doing clinical trials is usually beneficial.