Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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The Clinical Trial Process

Guest Expert:
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Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed and Francine welcome Dr. Sandra Alfano. Dr. Alfano is chair of the human investigation committee and associate research scientist for internal medicine at Yale School of Medicine. Here is Ed Chu.

Chu Sandy, thank you so much for joining us this evening and before we get into the meat of the matter, which is to talk about clinical research, can you give our listeners a little bit of your background, what got you into your current position at Yale?

Sandy I actually had a long career as a clinical pharmacist at Yale-New Haven Hospital and as part of that experience, for about 10 years, I served as a member of the Human Investigation Committee while I ran the research pharmacy for the medical center. I found the work fascinating and it gave me a very broad exposure to lots of different types of research taking place at the medical center and helped me to develop a number of collegial relationships with Yale researchers.

Chu Are you still involved in the pharmacy world, or are you just too busy with your responsibilities as chair of the HIC committee?

Sandy About five years ago, I did move from the pharmacy over to the School of Medicine to the HIC in a permanent role. So yes, I would call it busy in that role overseeing the work of the committee.

Foss Can you define for our listeners what the function of the Human Subjects Committee is?

Sandy We call ourselves the Human Investigation Committee, or HIC, here at Yale, but the broader term that people might encounter across the nation is the Institutional Review Board, or IRB. We have our special name at Yale, HIC, and that board or committee is a group of committed individuals who are responsible for reviewing, in our case, all bio-medical research at Yale. Dr. Chu mentioned the School of Medicine and the Cancer Center, and we also review the research for the School of Nursing and School of Public Health and Epidemiology, and our goal is to review research protocols prior to them starting. We will approve protocols that meet ethical standards and that are designed to protect the subjects that are participating in the trial.

Foss Sandy, there are national standards for how clinical research is being conducted, and what

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issues need to be reviewed in the protocols for human safety. Can you go through that a little bit with our listeners?

Sandy Back in the 1970s there was a problem in research, it was known as the Tuskegee Syphilis Trial and that problem called a lot of attention to the need for oversight of research and protection of human subjects, and that resulted in the passage of the National Research Act in 1974. That act established the IRB System in the United States, and following that a group of scientists and ethicists, and members of the public, met and issued our fundamental guiding document of ethical principles, the Belmont Report. And from that underlying ethical guidance, the regulations that govern human subject research were written and enacted in the late 1970s, early 80s.

Chu So all clinical research that involves human subjects then has to undergo this review by the HIC or other institution, the IRB review process.

Sandy That's correct.

Foss Can you tell us what that process is say from the time an investigator like Ed or myself would initiate or want to initiate a clinical trial, and submit it say to our departments for review? What's the process that happens at the institution to get that protocol to the final stage where patients can be treated?

Sandy As you can imagine protocols come from a variety of departments and each department has a different process, but when it feeds into the IRB, especially talking about clinical research involving drugs or devices or some intervention with humans, those protocols will go to the full committee, a convened group that meets and reads the entire proposal and the consent form, and will suggest changes or require changes before it will be approved. The things that the group will be looking for are firstly, a sound research design. The research has to be well designed in order to generate results. Those results can be either good or bad, and we do learn from both types of results but we want the protocol to be designed so that it will generate results. So we will look at the design of the study to see if it is sound according to scientific standards. We also will look at the ethical principles, the protection of subjects, which are built into the protocol. We have what is referred to as a data in safety monitoring plan where the researcher is expected to be on the look out for anything that is happening and monitor the study very closely, so that if something untoward does happen, we can quickly make changes or halt the study.

Chu Obviously your committee reviews a broad range of different types of clinical research, so

who makes up the membership? I imagine it must be a pretty diverse group of individuals who constitute your committee.

Sandy Absolutely, and that's a very important aspect. Actually the regulations that I mentioned earlier dictate that we have quite a bit of diversity in the membership of our group. We are required to have scientists, we are also required to have non-scientists, so there is a lay person's voice and a lay person's perspective heard on the committee. Naturally at a center like Yale, we are going to have people with a variety of backgrounds so that we will be knowledgeable enough to review the variety of protocols that come to us. But it's important that we have that balance between the scientist and the non-scientist ensuring that we are protecting the people involved in the research.

Chu You mentioned that you look at the effects of a given protocol, so do you have bio-medical ethicists who also serve on the committee?

Sandy Yes, we certainly do and it's important that the members be aware of the underlying ethical principles as well as the ethical hot topics or issues that are somewhat controversial in this country, so we want our members to also be aware and continually learning about those topics.

Foss As a member of one of your three committees, I think that you do an excellent job helping us as committee members to understand those issues and there has been an evolution in terms of the thinking about the ethics in some of these areas that are controversial, particularly what we do with children. Could you talk a little bit about the process of children, and how we get consent to treat a child on a clinical trial?

Sandy Children are considered what's called a vulnerable population. One of the features of getting consent from a research participant is that the person should make their own decisions. We believe in personal autonomy in this country, and so we want the person that will be in the study to make their own decisions. With children that is either impossible, or difficult, because children are not able to make their own decisions for most of the time that they are children. Of course adolescents, late adolescence, becomes a different situation, but if we think of younger children they would not be able to make their own decisions and so we are required to have special protections for children. Certainly, parental permission is what we use as our method of consent and we also will explain the study as best we can to the child and get the child's assent as well, but beyond the parental permission and the child's assent, there are stricter restrictions on what types of research we are allowed to enter children into because of this idea that they are vulnerable.

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Foss And there are other vulnerable populations as well.

Sandy That's correct.

Foss Can you talk about the others?

Sandy The National Research Act and the regulations that I mentioned earlier apply to all research and then there are three subparts that focus on special populations, one is children, as I just said, another is pregnant women that require some special safe guards, and the third are prisoners. So prisoners, again, if you think about their ability to make their own decisions, a person that is imprisoned is limited in their ability to make their own decisions, so we have special safe guards that must be in place. Those are the regulatory defined vulnerable populations, but we believe at HIC that vulnerability really extends well beyond those groups and could involve a number of groups such as people with decisional impairment, again, if they do not have the cognitive ability to make their own decisions then they are going to need some special protections. There could be other vulnerable groups, low socioeconomic status might expose people to undo influence.

Foss When we review these protocols, one thing that we do is look at what we call the level of risk, whether a protocol involves a low level of risk, or a high level of risk, and that to some degree affects our decision about the protocol particularly in those vulnerable populations.

Sandy That's correct.

Foss Our listeners probably don't appreciate that any clinical research, including things like questionnaires for instance, are considered clinical research and go through this committee.

Sandy That's right. I think it is important to understand that risk is inherent in clinical research, and we are often doing research to discover the side effects and toxicities associated with different interventions, and so it's important to recognize that risk comes along with research. Our job with the HIC and the job of the researcher are to try to minimize those risks. We really cannot target eliminating risk because we are doing research to discover them, so we want there to be features built into the protocol that will minimize risk. We will then, in the committee, review the whole of the protocol to see whether the risk is acceptable or not. Although we sometimes put levels of low, moderate, or high on the risk, it's always a decision about whether the risk is reasonable in terms of the benefit that may come from the research.

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Foss Thank you Sandy. We have to take a break now for a medical minute. Please come back and join us after the medical minute with Sandy Alfano, our guest for today.

Medical Minute *Over 170 thousand Americans will be diagnosed with lung cancer this year and more than 85% of these diagnoses are related to smoking. The important thing to understand is that quitting, even after a decade of use, can significantly reduce the risk of developing lung cancer. Each day patients of lung cancer are surviving thanks to increased access to advanced therapies and specialized care and new treatment options are giving lung cancer survivors new hope. Clinical trials are currently underway at Federally designated comprehensive cancer centers like the one at Yale that have innovative new treatments for lung cancer and patients enrolled in these trial are given access to medicine not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and our guest today is Sandra Alfano. Sandra is the director of the HIC, or the Clinical Research Office at Yale. We were talking before the break, Sandra, about the process of assuming or deciding about risk associated with various treatments or protocols, and that is a nice segue way into what I wanted to ask you about the whole process of informed consent, which is so critical when we do clinical research.

Sandy Yes, which stems back to the principle of respect for persons, which as I said earlier relies on personal autonomy in making decisions about whether or not you want to participate in research. In order to make those decisions, a person needs to be adequately informed about what's involved, what the risks are, what the potential benefits are, and then the number of other features about voluntary participation; what will happen if someone is injured, are there any costs involved? All of those features are included in what we would call the informed consent process. That is a process where a researcher will have a dialogue with a potential participant to explain these aspects of the research in order to allow them to make their own decision. One piece of that of course is a written consent form that includes all of that information and tries to explain in a written format the ins and outs of the research protocol. My committee, the HIC, will of course scrutinize those consent forms and try to work on the wording and try to make them as clear as possible for subjects. But there are two additional features that are really important, one is that dialogue of the researcher with the participant and during that dialogue there needs to be an assessment of the subjects understanding. Are they really getting it? Do they understand that it is research? Do they understand that it may

not directly benefit them? Do they really understand the risks involved with this research and are they making their own decision? So the researcher's assessment of understanding, and then ultimately the subjects understanding allowing them to make the decision, is really the key features of informed consent.

Chu On that point, I have been impressed that at many cancer centers where they see a fair number of say minority, underserved populations, that the HIC or IRB will develop consent forms that are in different languages such as, Creole, Spanish, even Chinese, and try and have interpreters to discuss informed consent and all of the various issues involved in considering going on a clinical trial to help facilitate the understanding process.

Sandy Absolutely, it is essential that the individual thinking about participating in the research get the information in a language that they can understand, so it is expected that a consent form will be translated into someone's native language if they are non-English speakers, but it is interesting, one of the difficult issues to accomplish when conducting research in settings such as the Yale Medical Center, is there are a variety of languages spoken and the resources required to translate all of the forms could be enormous, so that is one of the issues we struggle with.

Foss One of the other issues that we as a committee have struggled with is the whole issue of tissue banking, and all of the legal ramifications that go along with that. In cancer therapy there are great moves now towards personalized medicine, which means that we take portions of tumor from patients and we do various studies on them to try to identify say, which patients would be best for certain types of therapy, and this really involves a tremendous effort together, lots of tissues from lots of patient. Can you talk a little bit about some of the ramifications of tissue banking and how the HIC gets involved with that?

Sandy Absolutely, that is one of the ubiquitous issues that we deal with on almost every protocol now. Research has progressed so that we recognize that samples taken for routine monitoring of the patient during the trial may actually hold some information that will be very helpful to us in the future in better understanding the disease, or better understanding the treatments that we are designing. Most researchers want to keep whatever samples are collected, blood, bodily fluids, leftover pieces of tumor, the like, and will tell the participant in the consent form that they would like to keep those samples for future research and my understanding is that most participants will check, yes, that's okay. They have given their consent to allow that future research. One of the issues that then creeps up is what will that future research involve? If we are talking about cancer therapy, if a person has lung cancer and future research involves lung cancer, well that certainly seems fine. If the person has lung cancer and the future research is for another type of cancer, breast cancer, or some other type, that

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seems fine as well; it seems no one would object to that. Questions start arising when someone would like to do some research in a different disease, be it psychiatric disease, genetics, or something like testing IQ and trying to relate that to race. Some people might find that type of research objectionable, so I give that as an example where we certainly want people to give consent for use of their samples, but as science progresses it's difficult today to predict the type of research that might be done a year, five years, or 10 years from now, and so it becomes difficult to know whether it's still okay to use those samples.

Foss What happens if a patient consents to have their tumor sample or their blood sample collected, and then say a year or so later they decide they don't want their sample used for research, what happens at that point?

Sandy That's a good question, and it relates to a fundamental right that participants have when participating in research to always withdraw from the research without any negative repercussions. So in your case, someone that's given a sample a year later says, 'Gee, now I am starting to worry about my stuff out there and I want it taken out of that research.' They have that right and they should be told of their right in the consent form. That's an element that we will always include and they can call and have the sample withdrawn from any further research.

Chu Following up on that issue, it is important to emphasize to our listeners that if say they are coming to Yale Cancer Center to enroll in a clinical trial that say Dr. Foss or myself have, if for whatever reason they decide that they don't want to continue on that clinical trial, they can stop, they have that right.

Sandy That's right. Now, when we have people participating in medical trials and treatment trials, it is often very important that they work with the researcher and not just abruptly stop. There may be lingering drug side effects or there may be different therapies that they need to transition to, so we would never recommend that someone just walk away without working with a researcher, but we absolutely want participants to know that they have the right to withdraw without any negative repercussions.

Foss Sandy, just to touch on another point, with respect to protection of a patient's identity, could you go through the safeguards that are in place say for a patient whose tissue goes into a study, in terms de-identifying them at further points if research is done on that tissue?

Sandy That is an important element that we want to safeguard; privacy and confidentiality. That has always been a feature of medical practice to treat patient information confidentially, but of late and since the mid 1990s, there has been attention to transmission of medical data across

the nation. There are good and bad features to having sharing of medical data, but one could be invasion of privacy, so in clinical trials we always are attentive to safeguarding privacy and confidentiality. Most of the records that are kept are kept in a coded fashion, they don't contain the persons name or direct identifiers, but they have some sort of code so that we could link back to the person and the person's medical records. If tissue is stored, tissue or blood or any of those samples, they generally are, as you said, de-identified. We don't want, you know, Sandra Alfano on the test tube, but rather there would be some code that could be linked back to my records.

Chu In the remaining sixty seconds that we have left in the show this evening, can you tell our listeners that are interested in learning more about the conduct of clinical research, learning more about what your very important committee is doing here at Yale University, how they can gain access?

Sandy` The HIC is part of a larger human research protection program at Yale and we have a website, www.yale.edu/hrpp and that has a very richer array of research participant materials that our listeners might want to look at.

Chu It's been great having you on the show. I know I have learned a great deal about how clinical research is ongoing. Unfortunately, we did not really have a chance to talk about the wonderful interactions, the relationship that developed between Yale Cancer Center and your committee to facilitate the conduct of clinical research, and hopefully the next time we will have you back on the show to talk a little bit more about that.

Sandy Thank you.

Chu It has been great having Dr. Sandra Alfano as our guest expert on Yale Cancer Center Answers to give us a wonderful overview of the conduct of clinical research. Until next week, this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

If you have any questions or would like to share your comments, visit yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.