FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

QUALITY OF LIFE SUBCOMMITTEE

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

8:05 a.m.

Thursday, February 10, 2000

Ramada Inn
8400 Wisconsin Avenue
Bethesda, Maryland

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ROBERT JUSTICE, M.D.
RICHARD PAZDUR, M.D.
ROBERT TEMPLE, M.D.
GRANT WILLIAMS, M.D. (AM session)

ALSO PRESENT:

DR. RICK BERZON, Boehringer-Ingelheim
DR. WILLIAM LI, The Angiogenesis Foundation
KATHERINE MEADE, National Prostate Cancer Coalition
WILLIAM ROSEN, Cure for Lymphoma
GEORGEA SACHER, Colorectal Cancer Network
PAULA SIMPER, Pancreatic Cancer Action Network
SUSAN WEINER, The Children's Cause, Inc.
RICHARD WILLKE, Pharmacia & Upjohn

C O N T E N T S

C O N T E N T S (Continued)

PROCEEDINGS

(8:05 a.m.)

DR. CELLA: Good morning, everyone, and welcome to the first of an as-yet unknown number of meetings of the Quality of life Subcommittee of the Oncologic Drugs Advisory Committee, convened at the request of the Food and Drug Administration.

I'm David Cella and I'm Chairman of the subcommittee. In just a moment, I'll ask the members around the table to introduce themselves, but first I'd like to say a few words of introduction really meant to establish and clarify the current purpose of this subcommittee, at least as I understand it. We will hear more about that from Dr. Schilsky in a moment. I want to include in there the ultimate objective of the subcommittee, but also the specific goals for today.

The ultimate goal of the subcommittee is to advise and assist ODAC in its review of quality of life and other patient-centered, patient-reported outcomes that are submitted in support of applications for oncology drug approval.

Today's goal is not to conclude with the provision of this advice. The task that we're asked to do requires more than one meeting, and all of us around the table are well aware of that.

Today's goal is to clearly define the key issues to be addressed so we can accomplish our charge and set in place a procedure for moving our subcommittee as rapidly as is reasonable toward that charge.

I met with members of the Food and Drug Administration about a month ago, maybe a little more, to come up with the agenda for this first meeting. In that meeting, we agreed that there are three key areas that we need to focus on.

First, it's not meant to be a complete list. It's also not meant to be a mutually exclusive list, meaning there's overlap even across these three areas.

These three areas are definitional issues across the continuum of patient-centered outcomes, clinical significance and clinical interpretation of data, and analysis of data. Three of our subcommittee members, Dr. Carol Moinpour, Dr. Jeff Sloan, and Dr. Diane Fairclough, have kindly and generously agreed to stick their necks out and go as far as they could, within reason, to propose draft recommendations or at least suggest what are the key issues that need to be honed in upon to come up with those draft recommendations.

It is the goal of this subcommittee to have clear and concrete recommendations, as specific as is reasonable. But again, I don't anticipate that we'll be

voting or deciding upon any of these recommendations today.

Our next meeting is likely to be in June. There will be activity between this meeting and that meeting, and the specific date we hope to have pinned down by the end of today.

Discussing those three presentations that I just outlined will be Dr. Donald Patrick discussing Dr. Moinpour's brief presentation on definitional issues, Dr. Stacy Nerenstone discussing Dr. Sloan's presentation on clinical significance and clinical interpretation, and Dr. Nan Laird by teleconference discussing Dr. Fairclough's presentation on data analysis.

At the risk of alienating myself from my colleagues, I told them that I want them to speak for 10 minutes, which is really not enough time for any of these presentations, but in the interest of having as much time for discussion as possible, I persisted with that and said I would not get antsy until they hit 15 minutes, so giving them a little leeway, but I do want to be able to preserve ample time for discussion of these important issues.

At the end of the day, we will also discuss under the agenda heading called Future Plans for the Subcommittee several other issues that are listed on the agenda, as well as those that come up through the course of the day.

So, with that introduction, I'd now like to ask the committee members and the members of the Food and Drug Administration around the table to please introduce themselves. Why don't we start with Dr. Fairclough here and come around the U?

DR. FAIRCLOUGH: I'm Diane Fairclough and I'm learning how to use the mike.

(Laughter.)

DR. FAIRCLOUGH: I'm a biostatistician. I've been looking at outcomes in pediatric and adult cancer for pretty much all of my professional career. We finally labeled it as quality of life, but it has been something that has been important I think.

DR. NAIL: I'm Lillian Nail. I'm a professor at the College of Nursing at the University of Utah. My research is on coping with cancer treatment. One of the primary reasons I'm here is because I'm a two-time cancer survivor.

DR. PATRICK: I'm Donald Patrick and I'm a professor and head of the social and behavioral sciences program at the University of Washington School of Public Health in Seattle. I do health status and quality of life assessments and disease-specific and generic instruments.

DR. NERENSTONE: I'm Stacy Nerenstone, medical oncologist, a clinician from Hartford, and I sit on the

Quality of Life of the Gynecologic Oncology Group and I'm part of ODAC.

DR. PELUSI: I'm Jody Pelusi. I'm the consumer rep, and I am an oncology nurse.

DR. SLOAN: I'm Jeff Sloan, also trying to figure out how to work a microphone, from the Mayo Clinic, a statistician by training. I've done a lot of work in quality of life research, especially in the area of nursing research and measurement issues.

DR. DICKERSIN: I'm Kay Dickersin. I'm an epidemiologist at Brown University. I'm also a 13-year breast cancer survivor, and I've worked quite a bit in breast cancer advocacy.

DR. SCHILSKY: I'm Rich Schilsky. I'm a medical oncologist at the University of Chicago. I'm the current Chair of ODAC.

DR. CELLA: I'm David Cella, professor of psychiatry and behavioral science at Northwestern and Director of the Center on Outcomes, Research and Education at Evanston Northwestern Health Care.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary of ODAC, FDA.

DR. MOINPOUR: I'm Carol Moinpour, a psychologist with the Southwest Oncology Group Statistical Center in Seattle and I coordinate quality of life

assessments and our prevention and treatment trials.

DR. CHIAO: I'm Judy Chiao, medical reviewer in the Division of Oncology Drug Products.

DR. WILLIAMS: I'm Grant Williams, the medical team leader, FDA.

DR. BEITZ: Julie Beitz, medical team leader, FDA.

DR. PAZDUR: Richard Pazdur, Director, Division of Oncology Drug Products, FDA.

DR. CELLA: Thank you, everyone, and again welcome and thank you for coming.

Dr. Somers is going to read a conflict of interest statement now.

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Since the subcommittee's discussion of issues related to the study of quality of life for patients enrolled in cancer trials will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to all firms conducting research of drugs for the treatment of cancer, in accordance with 18 U.S.C., section 208(b)(3), general

matters waivers have been granted to all committee participants which permit them to participate fully in today's discussions. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12-A30 of the Parklawn Building.

In the event that the discussions involve any products or firms not on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

Thank you. I think that is a record short conflict of interest for an ODAC meeting.

DR. CELLA: Now I'm pleased to reintroduce Dr. Schilsky to you. Dr. Schilsky chairs the parent committee to this subcommittee, the Oncologic Drugs Advisory Committee, and he'll inform us on the ODAC perspective on the need for the subcommittee. Rich?

DR. SCHILSKY: Thanks, David. I didn't prepare a very formal presentation, but I have given some thought to the issues that this subcommittee will be discussing.

I think it's very timely that this subcommittee has been formed. We grapple with issues with respect to the quality of life components in applications that are

reviewed at ODAC all the time, and they are both enormously important and enormously complicated and sometimes very frustrating. I thought I would just briefly review some of the types of issues that we have concerns about in the parent committee.

Unfortunately, to some extent, it's relatively uncommon that studies of new drugs in oncology provide unambiguous evidence of a survival benefit. So, in trying to assess clinical benefit for patients who are enrolled in oncology drug studies, quality of life is becoming an increasingly important component of those types of applications and as a means of assessing clinical benefit for patients who are receiving one kind of therapy or another.

We've really not had as a sitting member of ODAC, at least during my time on the committee, I guess someone who is an acknowledged expert in quality of life research, although clearly we have ad hoc consultants on a variety of issues, as appropriate, during committee meetings.

We've all recognized that there are multiple dimensions to this thing we call quality of life. There are multiple assessment tools and multiple scales within those tools that are used as measures of quality of life. I think many of us who are clinical oncologists wonder

sometimes about the clinical relevance of changes in various scores on all of these scales that are often presented to us. What is the clinical relevance of a 2-point change or a 10-point change? How does that really translate into something that is a clinical parameter that we're more accustomed to dealing with in patients?

Because of the multiplicity of assessment tools and scales and scores, we run into difficulties with assessment of huge masses of data. It's not infrequent, of course, that sponsors come before the committee, having carefully selected elements of the data set to present to the committee, which inevitably are those elements that have the most positive outcomes with respect to the effects of their product. Rarely do we see all of the other elements of the assessment that may not be as positive. And it's difficult to determine sometimes whether the positive outcomes are truly positive or just sort of random associations that occur when you have such large numbers of endpoints that can be evaluated.

That's all further complicated by issues that are frequently raised by statisticians both on the committee and the FDA statisticians with respect to the need to adjust significance levels for multiplicity analyses in terms of what exactly is a statistically significant difference when you're looking at multiple

endpoints.

Things are further complicated by loss of data over time and the fact that that easily introduces bias into the evaluation of samples. Patients who are not doing well drop out early. Patients who are doing well stay on longer. They're the ones who complete quality of life assessments on a longitudinal basis, and so there's a tendency for the population to become somewhat skewed over time toward those people who are doing better anyway.

Another issue that I find particularly troubling is that it's relatively uncommon that the quality of life assessments that are presented as part of drug applications are actually hypothesis driven. More often they're purely descriptive and oftentimes they represent secondary and tertiary objectives in a protocol, so that the clinical trial design is often based upon the usual efficacy endpoints of survival or time to progression and it's those efficacy endpoints that tend to drive the sample size for the study.

Frequently then what happens is that as a secondary or tertiary objective, there are descriptive quality of life analyses added in often without any specific hypothesis being proposed by the investigators as to what quality of life changes might be expected to occur based upon whatever the treatment program is. As a result,

I think frequently the quality of life analyses are actually grossly underpowered because the sample size is really not adequate to detect statistically significant changes in multiple quality of life parameters.

So, that's another issue that I find particularly troubling because it seems to me that quality of life research should be subject to the same rigor and hypothesis-driven basis as all other elements of clinical research. I think we need to specifically address that in this subcommittee.

I also think it will be important for us to really talk about the need, if you will, for sort of global quality of life assessments as opposed to, for example, just evaluation of symptom improvement. Many clinical oncologists, I think, are pretty comfortable with evaluating symptoms like pain and nausea and also getting a fairly accurate estimate of performance status of patients. I think an important question for us to grapple with is what additional benefit comes from doing a more global quality of life assessment, above and beyond that which can be obtained from a careful analysis of patient symptoms and status.

It would be helpful I think to the committee -- in fact, to the investigator community -- if we could ultimately define a limited number of parameters or

assessment tools that provide consistently reliable measures, perhaps across multiple tumor types in patient populations, so that we don't have to be confronted all the time with multiple scales that are developed for specific tumors or specific stages of tumors or specific symptom subsets within tumors. It becomes really remarkably complex and an overwhelming task I think for many people to evaluate such enormous data sets and derive clinically meaningful results.

So, I would just conclude by saying that I think, as David said, an important ultimate goal for this subcommittee would be to provide guidance to the investigator community, provide guidance to industry, as well as to FDA, as to how to optimally design studies that will provide informative, reliable, consistent results that we can use in really assessing whether a new drug, a new therapeutic regimen provides true clinical benefit to patients.

So, I will stop there.

DR. CELLA: Thank you, Dr. Schilsky. That's very helpful, and you've raised several questions that I'm sure we'll return to over the course of the day. I'll try to bring us back to some of those as the discussion proceeds.

At this point now we would like to move to the

open public hearing part of the meeting. There are seven people who have requested time to express opinion or perspective, and the first is Paula Simper from the Pancreatic Cancer Action Network. Ms. Simper?

MS. SIMPER: Good morning. Thank you very much. My name is Paula Simper and I am here to represent what is a newly formed advocacy group for pancreatic cancer.

I'm sure you're all aware about pancreatic cancer being one of those cancers that's a deadly one. Just to share a little bit as far as who and what, it's a cancer that affects 29,000 people a year, approximately. It's the fourth leading cause of cancer death for both men and women in this country. It's a disease that usually strikes very silently and has the highest mortality rate of all cancers at 99 percent. Most of the patients do not live beyond a year, and their quality of life is very poor. It's poor because the disease itself is very aggressive, and so it's the effects of the cancer itself, but their quality of life is also poor because, unfortunately, there are very, very few treatments available for pancreatic cancer. So, it's a little bit of insult to injury in terms of having anything available to them.

There is no cure at this point. There is no early detection. So, they're left with a very terrible set

of circumstances to deal with.

Therefore, quality of life becomes extremely important for this particular community because, as many of the doctors have said to us, their patients say to them, well, I realize I have this prognosis, I realize that it's terminal, but can we try and make it as nice as possible while we go through this journey where we know where the end target is. One of the biggest struggles that the doctors are dealing with is how to help these people maintain their dignity in what is a really difficult situation and dealing with the end stages of their disease to try and maintain some sense of quality of life. In many instances, these people are given a diagnosis and then three to four months later, that's it. So, that time that they have shrinks and shrinks and they need good quality time for that.

Why do we need to be doing this? Because we have a population that is increasingly aging and we're going to be dealing with a lot of people that are going to demand, and we demand good quality of life.

Quality of life, if we can include this as an endpoint, will allow a more comprehensive approach. It includes being able to have a physical and a mental component to all of the care, and not just looking necessarily always at this clinical benefit and outcome.

There are studies that have shown where certain aspects of improving things such as pain management can affect survival outcome. There was a study done by Dr. Keith Lillemoe, one of the surgeons at Johns Hopkins, talking about pain management subsequent to whipple surgeries. His study clearly demonstrated increased survival. So, I think that if we look at the big picture, there can be benefits derived from that.

We have an obligation and a responsibility to provide good quality of life the best that we can.

The questionnaires and the measurement assessments that have been developed over the past several years are improving. They need to get better, but they are improving.

So, what we need to do at this point is we need to look at what the barriers are or what the obstacles are to achieve better quality of life assessment and how to include that in the overall picture. We need to find the weak spots such as the areas that tend to skew the data like missing data and things like that. We need to figure out how to fix that so that you can fix those problems.

People talk about the increased burden of the investigators having to have additional costs and monitoring and all these things that go with that. That may be so, but I think what needs to happen is there needs

to be training and there needs to be a system set up in place that these people are given the support, the clinicians and the data managers. They need the support to be able to provide the data. I think they all work very hard at what they're trying to do, but sometimes there is a lack of support, tools, and resources that allow them to do their jobs correctly.

Then what we need to do is the data needs to be reliable. It needs to be valid. The way that that can be accomplished is in the beginning a really good system has to be set up where you establish good criteria, solid criteria, meaningful criteria, and then you take that and then you develop that into the analysis methods that you need.

So, how we do this is taking advantage of technology available today. Much of the data that's collected and much of the methods that are used are really very old-fashioned. They need to be brought forward and they need to take advantage of the technology. We have a lot of technology at our fingertips. Yes, sometimes systems that are this large are slow to respond, but we need to use the technology available to us because then, in turn, the results will generate themselves down the road.

We have to innovate. We have to strategize better on how to analyze the data and then how to use the

data.

When a cancer diagnosis is given, in many of the instances, fortunately due to good science and due to clinical trials and due to these things, cancer is not always a death sentence. It is oftentimes an acute disease that can become a chronic disease, which is good progress.

In the case of pancreatic cancer, though, we don't have that progress at this point. We have a diagnosis and then we have death. So, either one, whether it's going from acute to chronic or diagnosis to death, it really doesn't matter because all types deserve quality of life because just because you have a diagnosis doesn't mean that you should lose hope and it doesn't mean that you have to suffer from poor quality of life.

So, on behalf of our community, we would greatly encourage you to strongly consider including this because I guess the way that we look at it is, yes, there is a thing as the primary endpoint and all the clinical definitions of everything, but there's really more than one way to skin a cat. So, what we need to look at is how offer the best. Particularly to those with this type of disease, it's a tremendous burden.

Thank you very much.

DR. CELLA: Thank you very much for your perspective and your advice and support.

The next speaker will be Katherine Meade from the National Prostate Cancer Coalition.

MS. MEADE: Thank you, Dr. Cella and distinguished panel members.

I'm here before you today because in August of 1998 my husband died. He was suffering initially from prostate cancer and then a second primary cancer in his lung. We were very lucky because, throughout the entire course of his illness, he never spent one night in the hospital. I was his primary caregiver and also his partner in dealing with his disease. We went to the doctor appointments together and researched the disease together, got involved in support groups together. From my own experience and from what I have learned from others in similar situations, at least with prostate cancer, it becomes a family disease. I feel as if I have studied enough to be given some sort of honorary masters degree in prostate cancer.

After Bill's death, I found it difficult to pull away from the many friends I had made in the prostate cancer community. I continue to be involved as an advocate for various issues that impact the patient and his family.

Throughout the years of my involvement, quality of life has always been a major issue for most of the people dealing with the disease. When you first get the

diagnosis of cancer, you function in a fog, pulling together information on treatment options. You focus so heavily on a cure. You want the disease to be gone. As you adjust and learn to live with the disease, you often see a shift so that quality of life issues become more and more important. I think that this is especially true since often the patient lives for many years and because treatments have such severe and life altering side effects.

Let me share with you some of the life altering side effects men with cancer have to deal with: impotence, incontinence, hot flashes, fatigue, bloating, loss of appetite, loss of libido, depression, distractibility, memory problems, irritability, and the one I hear the most jokes about, the growth of breasts. These are just some of the changes that men and their families face together when they are burdened with this disease. There must be a solution to improve the quality of life that is so diminished during this experience.

Patients and their families try all the standard treatments for these side effects and often resort to dietary changes, to herbal and vitamin or other supplementary treatments. These are often related to controlling the side effects more than actually treating the disease. Very rarely are men sorry that they had treatment, but soon alleviation of the side effects takes

up much more of the conversation than curing the disease. If you listen to the chatter at support groups, often people are discussing what others take for hot flashes, or if they know anything that will strengthen your bones, or the one that is talked about more quietly, is there anything to take for impotence.

The men and their families most often learn to live with depression, irritability, distractibility, or memory problems. It is less often discussed, but now I'm beginning to hear more conversations about control of these side effects that impact so subtly the family's quality of life.

More research has been done recently on prostate cancer, and survivors are reading and awaiting a medication that will give them an alternative to the standard hormone therapy that is given commonly to men who are or may have metastasized cancer. As alternatives as are developed, I beg the scientists and researchers to look at the side effects and find a way that they can be minimized without impacting the effectiveness of the treatment. In addition, if there are medications that will help alleviate some of the side effects listed above, it must be realized that while they may not kill cancer cells, they will make the time the patient and his family have left much more meaningful. They will not be distracted by

side effects that take away from their quality of life. Patients and their doctors are constantly balancing between a cure and quality of life. Anything that the FDA can do to make the tools available to do that more easily would be very, very valuable to the patient and his family.

Since so many of the side effects for prostate cancer patients are similar to problems experienced by menopausal women, is it possible that drugs used to treat these women can be tested on men with prostate cancer also? Just recently there was a new drug mentioned for building bones in women with osteoporosis. Would it be possible for the FDA, when testing new drugs of these types, to investigate whether they might be useful also by men dealing with prostate cancer?

During end stage disease, the issues are often similar to the side effects that are dealt with during the early stages of the disease, but they may become gradually more severe. In addition, general weakness is added to the list of problems, along with a loss of taste and the general enjoyment of food. Another complaint that is relatively common is neuropathy and the discomfort that can accompany it. As the bones weaken from combined hormone therapy and from metastasized cancer, pain increases and breaks in the bone occur. Often these breaks are not caught immediately and the patients are in severe pain.

The other problems such as fatigue, loss of appetite, irritability, loss of memory, incontinence, and fecal incontinence become more and more of an issue. The focus at this time seems to switch to pain relief. This is an issue that has received much press in recent months. We were lucky. Our doctor was skilled in understanding how to prescribe pain medications, and eventually we dealt with the hospice people who understood pain medication better than any other professionals that we dealt with through the entire course of Bill's illness.

My observation in this area for improvement is outside of the direct control of this group, but what I experienced was that education needs to be done in the patient community, as well as in the physician community. Too often people are under-medicated or over-medicated, and with a skilled practitioner, most people I have known can have their pain controlled and still be aware of what is happening around them.

Prior to coming here today, I spoke with Dr. William Nelson at Johns Hopkins. He told me that what I needed to do was to speak to you from my experience and to make myself available to you if you have any questions. As he said to me, new drugs can improve the overall quality of the time the patient has with his family. They can provide more good days and that is so important to the patients and

their families. I have good memories even of the last days when Bill felt most comfortable and his pain was under control. Death is not easy but it does not have to be a horrible situation, and medications and quality of life issues play a major role in giving people with cancer the ability to live their lives to the fullest with the time that they have left and to die in peace with dignity.

Thank you for giving me your time.

DR. CELLA: I'm sure I speak for the rest of the subcommittee when I say these are very moving and powerful presentations. Thank you very much. You begin with a very personal statement but really speak for the many, many people.

Dr. William Li from The Angiogenesis Foundation.

DR. LI: Well, thank you, Dr. Cella, and good morning. I'm Dr. William Li, the President and Medical Director of The Angiogenesis Foundation.

The Angiogenesis Foundation is a nonprofit organization whose mission is to facilitate the development and application of new angiogenesis-based medicines. And for the past five years, we've served as an information clearinghouse in the field, a research and education institute, and as a think tank for drug development. We've also been studying how to optimize clinical development of

angiogenesis modulating drugs, both inhibitors and stimulators, including the identification of appropriate clinical trial endpoints. Today I've come to bring this ODAC subcommittee our views on quality of life as an efficacy standard for the approval of new cancer drugs.

Angiogenesis, the growth of new blood vessels, is a biological process used by tumors to recruit their own private blood supply. Antiangiogenic therapy is a new approach to treating cancer aimed at inhibiting the vascular endothelial cells that support tumor growth. Antiangiogenic drugs represent a new class of cancer agents known as cytostatic agents which prevent tumor expansion and stabilize disease. This paradigm shift away from the wholesale destruction of proliferating cells with highly toxic agents requires new tools for evaluating agents in clinical trials.

For example, reduction of tumor size, a classical benchmark for tumor response to cytotoxic drugs, may not be the best primary endpoint for cytostatic agents. Instead, stable disease may be a more realistic and desirable endpoint. Tumor mass may stabilize with antiangiogenic drugs and suppression of metastases may require chronic or lifetime therapy. Therefore, clinical trials of cytostatic agents should focus on patient survival, time to progression, and importantly quality of

life as markers for efficacy.

Another change brought about by antiangiogenic therapies is that quality of life measures may be in concordance with therapeutic benefit. Antiangiogenic drugs as a class are generally well-tolerated and maximally tolerated doses of a drug may not be required for the optimal biological effect. Now, without the well-known toxicities of traditional chemotherapy, a cancer patient's perception of quality of life may be more aligned with the benefits of stabilized disease, such as preserved function and enhanced sense of well-being.

Investigators and sponsors of antiangiogenic drug development for oncology acknowledged the need to obtain quality of life data. As of February 1, 2000, there are now 30 antiangiogenic drugs in phase I clinical trials for cancer, 25 agents in phase II, and 10 agents in phase III. Most studies include some type of quality of life assessment, but there is no standard instrument being applied across the board to allow for comparison or for benchmarking.

A standardized, scientifically designed, uniformly implemented quality of life instrument would be invaluable in our field for three major reasons. First, quality of life is a critical measure of the anticipated biological outcome of cytostatic agents. Second, quality

of life standards would allow the comparison of the benefits of different classes of agents, such as antiangiogenic drugs versus cytotoxic chemotherapies. And third, quality of life standards would allow for the comparison of one agent against another within their same therapeutic class.

Now, with these rationales in mind, The Angiogenesis Foundation would like to make five recommendations to this ODAC subcommittee.

First, we believe that quality of life is an appropriate standard endpoint for new cancer drug trials because, in addition to the biological reasons previously mentioned, patients prioritize quality of life in their cancer care.

Second, quality of life instruments must generate data that share the characteristics of an objective endpoint, that is, reliability, reproducibility, validity, responsiveness, and sensitivity, because of the inherently subjective nature of symptoms. Additionally, the placebo effect must also be carefully studied.

Third, no single quality of life instrument is likely to be applicable for all types of cancers due to their different locations or to all populations of cancer patients due to different ages. Multiple instruments are likely, therefore, to be needed to take these differences

into account, as well as to take into account different types of study goals.

Fourth, we recommend that quality of life instruments contain patient preference-based measures. By this, I mean that the data must reflect the practical considerations of a patient's life and be interpretable in terms of a patient-centered frame of reference.

Fifth, absolute rigor is required in the collection of data from all patients. One of our expert panelists performed a case study, based on available data from an angiogenesis clinical trial, in which 10 percent, 20 percent, and 30 percent of patients were removed as "data dropouts" to reflect a real-life scenario in which the sickest patients are those most likely to miss follow-up visits. As data from the worst patients were deleted, the quality of life measures appeared improved erroneously; whereas, in fact, this type of non-random censoring leads to false conclusions. Therefore, meticulous attention is needed for collecting data from every study patient, a step which is more likely to be followed if quality of life measures are part of an efficacy standard.

Finally, quality of life data can serve as a determinant for cost effectiveness of new cancer therapies. Like all new medicines, the first antiangiogenic drugs will be expensive due to the enormous cost of pharmaceutical

research and development. Rigorous quality of life data, showing preserved function, decreased hospitalization, less work missed, and improved emotional well-being, among other parameters, will eventually be used in our health care system to justify the expense of new forms of therapy.

In closing, The Angiogenesis Foundation strongly recommends that quality of life be included as an efficacy standard for the approval of new cancer drugs. New cytostatic strategies, such as antiangiogenic therapy, are changing the paradigm for treating cancer from an acute treatment with toxic agents to a chronic treatment with better or well-tolerated drugs. Patients, oncologists, and industry sponsors await guidance from the FDA about which quality of life measures will be acceptable for use in order to speed the approval of safe and effective new drugs.

Thank you.

DR. CELLA: Thank you, Dr. Li. If you'd like to make your written comments -- I notice you have them written, it seems -- available to the committee -- oh, I didn't see them. Thank you very much. I guess they're in the folder.

Georgea Sacher.

MS. SACHER: Sacher.

DR. CELLA: Sacher. Excuse me. I apologize.

Georgea Sacher from the Colorectal Cancer Network.

MS. SACHER: I've been called worse.

DR. CELLA: You've been called worse. Thank you. I feel better now.

(Laughter.)

MS. SACHER: Good morning, and I want to thank you very much for including our new organization, CCN, Colorectal Cancer Network. We're new on the map. So, thank you all of ODAC.

I am a survivor of third stage colorectal cancer. So, I'm not only glad to be here; I'm glad to be anywhere.

(Laughter.)

MS. SACHER: But I was diagnosed in May of 1996, so I'm approaching my fourth year. I don't think I ever had the attitude, though, that I was going to die. I just felt it wasn't my time yet. So, I was a real fighter and an advocate.

My main speech is not about drugs, so I have to put a little plug in. Mostly I go out for CCN and speak about colon screening. So, I want to say one thing a little different from the others in that colorectal cancer can be diagnosed early and sometimes prevented with the proper screening and early screening. So, there is where it's a little different from like pancreatic. We always

say no symptoms are a symptom. I did put some brochures out on screening, my favorite subject.

But meanwhile, someone like myself did get third stage, and then there are a lot of people I meet that have the fourth stage. Of course, we're mostly concerned about them and their kind of quality of life.

I must say they didn't bring me here today, but I must say the CCN has been funded by Pharmacia & Upjohn, and Genentech recently gave us funds too.

We're a little bit unique. Besides advocating colorectal cancer and awareness to the public, we're the only ones so far that have support groups. We're starting to get it nationally. The main one now is in Kensington and I'm going to start one in Virginia.

It's so important. I know when I was diagnosed, I had nowhere to go. If you had an ostomy, you had a support group; otherwise, forget it. And that shouldn't be. So, we have support groups not only for the patient, but also for the caregiver because they have different issues.

CCN feels that the present standard treatments for colorectal cancer are quite disabling and too restrictive. Most people get 5-FU and leucovorin. I got the jackpot. I got 5-FU, leucovorin, and levamisole. So, I don't know if I got more side effects from that because I

didn't have the other problems. But whatever I got was on a random study.

Anyway most of us experience the nausea and the vomiting and sometimes have to go to the hospital because you're so dehydrated, the skin cracking and sometimes bleeding. That's another one of the side effects of the cancer treatment for colorectal cancer. I have seen people where the white blood cells were so bad, and then you're being set up for infections when your white cells are so low.

So, to get back to someone that might have the fourth stage, which we have several in our support groups, we don't know who's going to live or who's going to die. That's up to God. On the other hand, when you do have fourth stage, you are fearing death. So, we're worried especially for them about the quality of their life and what drugs can be helpful to them. It's the old issue: harm versus benefit. I always feel like the way we're killing cancer is like poison killing poison, and I think we need to get away from that and add to drugs that will promote comfort not torture. Particularly keep in mind when you're making your decision, somebody might be on their last year of life, so we want to make it as palatable and as comfortable as possible. I believe that AIDS patients, especially toward the end, have had palatable

treatments, so we want that for cancer patients too.

So, we're all looking forward to finding some kind of solution for the quality of life in your drug program so people are not completely dehydrated.

Along with all these side effects can come depression, and you get into family issues and the whole thing. So, all I can do is stand here and say, on behalf of CCN, we please encourage you to find some drugs that will save lives and not destroy them.

Thank you very much for having us be represented.

DR. CELLA: Thank you, Ms. Sacher. We're glad you're here too. I noticed on your letterhead you have a club called the Semicolon Club.

(Laughter.)

MS. SACHER: Right. That's our support group.

DR. CELLA: A great name.

MS. SACHER: Yes.

DR. CELLA: Next is Jan Maryak from the American Federation for Urologic Diseases. Is Ms. Maryak or Mr. Maryak here?

(No response.)

DR. CELLA: We can check back at 1 o'clock again after lunch.

Nancy Roach? Is Nancy Roach here?

(No response.)

DR. CELLA: All right. We'll check back for Ms. Roach after lunch as well.

Dr. Somers will read Margaret Volpe's letter.

DR. TEMPLETON-SOMERS: "Dear Committee Members: Thank you for allowing me to submit this statement to the committee. As a breast cancer survivor who has participated in a clinical trial, I am extremely interested in quality of life issues impacting patients undergoing cancer treatment. The points I am about to make come from my own experience, as well as from women whom I have counseled as part of my volunteer activities for a breast cancer support organization.

"It is imperative that patients be provided with information regarding all possible side effects and the severity to be expected of these side effects prior to beginning either treatment or a clinical trial. Not only is time to progression or disease free survival an important measurement of efficacy of a new drug, but the patient's quality of life both during treatment and following treatment must be considered. A drug may so destroy normal cells that daily activities are curtailed.

"I believe the following points must be considered in measuring the efficacy of new cancer drugs, or for patients involved in clinical trials.

"1) Cardiotoxicity: Not only should deaths be measured, but the amount of possible damage to the heart muscle should also be measured, and patients so informed. Not only can cardiotoxicity limit a patient's daily activities, but someone who is very active physically may choose to forego a drug that might prevent them from permanently participating in their hobbies.

"2) Neuropathy: Many of us are told we might have some nerve damage, but the degree of damage should be measured. Quality of life is definitely impacted when a side effect of treatment is hearing loss and so much damage to nerves in the legs that a previously ambulatory patient must now resort to a walker or wheelchair.

"3) Anemia/fatigue: Severe anemia may result from some treatments. The length of time it takes the average patient to recover from anemia should be measured, and the patient so informed. Even though transfusions of packed red cells may be administered, as well as Procrit, the resultant fatigue can be overwhelming.

"4) Neutropenia: Severity of neutropenia must be considered. Physicians should be encouraged to make wider use of G-CSF, in order for patients to complete treatment more quickly, with less chance of low white counts and fewer infections. This would improve patients' quality of life.

"5) Low platelet counts: Some treatments may cause very low platelet counts, which may require a long recovery time. Currently there is no drug available to raise platelet counts. Quality of life is definitely impacted, as the patient has to be extremely careful to prevent bleeding.

"6) Pain: Not only is there pain associated with some of the above points, but after awhile, the patient is tired of all the needle pricks, gastrointestinal problems, and being poked and prodded. The length of time required for a course of treatment and any attendant pain must be measured.

"In summary, I strongly believe quality of life issues must be considered when new drugs are reviewed for approval as new cancer treatment. I urge you to consider the points listed above when new drugs are in the approval process.

"Thank you very much, Margaret Volpe."

And Mrs. Volpe's letter and Dr. Li's letter, which I did receive ahead of time, are available for viewing in the notebook at the table at the registration desk for those of you in the audience who would like to see them.

Thank you.

DR. CELLA: Well, that concludes this first

open public hearing session. I just want to make a brief statement, just a reaction to all of the presentations. Really, what do you say, subcommittee? Could we ask for more support? Could we ask for more clear-cut, universal demand that we do something to help the FDA in moving forward in this area? There was nothing but strong enthusiasm for this.

Admittedly, the term "quality of life" is a bit like apple pie in that it's hard to construe a negative argument, but I can assure you that those of us who are involved in this work, there are plenty of negative arguments that are available for discussion and probably will come up today for why it should not be included or perhaps may not be believed by some to be ready for inclusion in formal evaluation in drug approvals.

So, are there any comments that any other subcommittee members might like to make or anyone from the FDA before we proceed with the next session?

(No response.)

DR. CELLA: Okay, well, we're right on schedule. That's nice. Thank you again to all the speakers for your encouragement and your direction.

Now we'll move to the first of the three primary discussion areas in the meeting, and Dr. Moinpour will discuss definitional issues across the continuum of

patient-centered outcomes. As I mentioned, it will be roughly a 10-minute presentation really to lay out the issues. Then Dr. Patrick will offer a brief discussion, and then we'll have plenty of open time for a subcommittee discussion.

Carol.

DR. MOINPOUR: Thank you, Dr. Cella. I'm pleased to be here and be a member of the Quality of Life Subcommittee.

I've been asked to summarize how quality of life is defined, and I'm going to address this in terms of four issues.

One is that quality of life itself is a subjective construct in that we believe in most cases that the patient perception is the critical issue.

We also talk about whether or not quality of life is just health-related or whether it is a broader construct, and I'll be expanding on that. We, in general, in cancer clinical trials have primarily talked about quality of life really as measuring health status.

Also, the issue of how comprehensive does quality of life have to be in terms of how broad the impacts are on the patient. Which domains or dimensions are relevant?

Then the last point is something I'm not going

to spend a lot of time on, but the quality of life field has been criticized for not being theory driven in the sense that the explanation of the impacts on quality of life are not based on psychological or sociological theories, that predicted relationships among quality of life domains and hypotheses about the impact of treatment don't come from psychological theories. I'll talk just a little bit about that issue, and this is related to Dr. Schilsky's point about the need for hypotheses.

I'm sticking my neck out and making specific proposals for the work of the committee in the future.

The first one is, I think, pretty easy, that we do believe that the expert, with respect to patient benefit in new oncologic drugs or applications for different uses of drugs, is the patient him or herself. That person, the patient, is best equipped to evaluate claims about the impact of treatment. The subcommittee, however, may need to address when and if proxy ratings given by either family members or health care providers are appropriate.

Now, the quality of life versus health-related quality of life issue. I believe that in this field, particularly in cancer clinical trials, we have come to the conclusion that it's just not feasible to measure the myriad of non-medical influences, and we all know there are many on what affects our life. So, there is I think a

general consensus that we should restrict the measurement of quality of life in cancer clinical trials to the quality of life domains, the domains of functioning, that are likely to be affected by medical intervention. A term to describe that is health-related quality of life, which Dr. Patrick who's on our committee is associated with use of that term.

Now, there is what we can call an attribution problem when you try to get patients to just indicate the impacts on their life that are resulting from treatment. So, the question is can people actually separate the various sources of impacts from treatment and other influences in their life. So, actually what we do is not actually technically ask them to do that. We ask them to report about their current status, and in that way, we're not asking them to do this attribution.

To some degree, randomization in phase III trials addresses the unmeasured factors.

Now, the third point on this slide is the issue of can we combine the quality of life with quantity of life, with survival. This is an active research stream and an active research issue that addresses quality adjusted life-years or qualities or other indices or those incorporating utilities that summarize how duration of life is modified by how well you live, involving impairments,

functional status, perceptions, and opportunity, all of which is influenced by disease, injury, or treatment, and policy. This is a definition that was offered by Drs. Patrick and Erickson in 1993.

At issue -- and I think a good discussion for the work of the committee over the coming months -- is how well the utility concept incorporates patient perception and how comprehensive the utility rating is.

So, the proposal, with respect to quality of life versus health-related quality of life, is that we do in fact restrict quality of life assessments to health-related quality of life, that we ask patients to report their current status, and we ask the industry to try to address known covariates in the analysis when this is possible, and that health-related quality of life can include duration of life. It's a complicated question deserving our attention, but it is a fruitful area for research.

Now what I'd like to do is just talk a little bit about this comprehensive health-related quality of life, what domains or functions have people looked at when they've been assessing this area. This table is really a summary because there are many researchers and many questionnaires other than what I have mentioned here. Actually I abbreviated Dr. Neil Aaronson's name to fit on

the slide, and Dr. Cella's work with the FACT. Then the NCI stands for a report of a meeting that the NCI had in 1990 for assessing quality of life in cancer clinical trials and the recommendations that came out of that workshop. And then Dr. Leidy and his colleagues just published in January a very nice paper evaluating the validity of quality of life claims for labeling and promotion.

So, what I have done is put X's in the areas that people seem to say these are really the important areas of quality of life. Usually physical, psychological, and social, and symptoms, and then there's a functional or role functioning component that has also been addressed.

Symptoms I want to come back to because we think this is a very important issue in measuring comprehensive quality of life.

And then global. There's a lot of discussion about whether or not there needs to be a separate global measure of quality of life other than the total score.

This slide shows the many different kinds of domains that could be assessed in any kind of quality of life instrument. You see that it's much broader than what I had on my previous slide. Notice like the family well-being is something that is addressed in a number of cancer clinical trials, and Mrs. Meade's presentation certainly

pointed up the importance of the burden on the family, the impact on the family. It is a longer list than what I just showed previously.

Inclusion of symptoms is important because the symptoms help corroborate the physician-rated toxicities that are always included in clinical trials. They document palliation in advanced stage disease in particular. We need to not just look at symptoms, but to examine the reach of the improvement or deterioration in symptoms with respect to the general functioning mentioned on the previous slides.

Then with respect to why would we want to measure -- and addressing Dr. Schilsky's comment earlier about why would we want to look at these broader domains of functioning, we believe that if you have information, aside from symptoms, that you can have more specific information about how treatment affects patients, that the information informs patients and physicians about the risk/benefit tradeoffs associated with treatment.

Then I think a very important point is, aside from providing outcome information, the broader quality of life assessment can identify ways to improve cancer treatments. And we have several examples of that happening. Dr. Sugarbaker and Barofsky -- that's the famous one that everyone talks about where the trial with

soft tissue sarcoma involved changes in radiation treatment with resultant improvement in quality of life. And Dr. Harvey Schipper has talked about reducing the frequency of chemotherapy cycles requiring hospital or outpatient clinic visits to reduce the impact on patients or functioning, just having to come so many times to the hospital. And the Volpe letter addressed the issue of the length of treatment.

So, the proposal for what should be included in a health-related quality of life assessment would be that those assessments include psychological, physical, and social functioning of the patient. There is some discussion that needs to occur with respect to the need for a separate assessment of overall global quality of life versus just the total score. And then the measure should also include symptoms, but the symptoms should not just be reported in terms of those data by themselves, but that there should be an attempt to document the effect of change in symptoms on these other domains at the top of the slide.

And then some more about symptoms. Symptom status is not a manifestation of patient health-related quality of life, that symptom outcomes alone should not be called health-related quality of life. Symptom outcomes alone could be appropriate in a phase II, single institution or maybe a supplemental submission. And

symptom outcomes can also be designated primary, but by themselves, we're saying they do not reflect health-related quality of life, or I am proposing for the committee that would be the case.

Clinical issues, by and large, need to drive the content of the symptom measures. That is, you may have a set of items that are not measuring a unified construct and may show poor reliability but, from a clinical standpoint, are very important to monitor in a particular trial, particularly when different treatment arms have different toxicities associated with them. So, I think the symptom measure has to be driven by the clinical issues.

Now, on the issue of the role of theory, psychological or social science theories usually are not driving health-related quality of life assessment design. A psychometric theory has certainly done this in terms of measurement, but researchers such as Dr. Sonja Hunt have really taken the quality of life research field to task for not having actual psychological theories driving how we sort of present the construct of the impact on quality of life.

But I believe that what we've operated from primarily is that the first obligation is to look at what we expect from the treatment in affecting health-related quality of life for the patient, the issues that are

critical to evaluating that treatment. This can suggest broad impacts on the patient as well as symptoms and toxicity. The rationale for the treatment doesn't usually take into account the effect on these broader areas of quality of life, of patient functioning.

So, I think I'm going to stop there. How did I do?

DR. CELLA: You did great. Thank you very much, Dr. Moinpour. Carol was kind enough to list a few important additional slides in the packet that are there for discussion later or for clarification, but let's move now to Dr. Patrick's discussion.

DR. PATRICK: Thank you, Carol, for giving us such a nice start to the definitional issues. It was wonderful.

I think Carol made a number of very important points. I want to say that part of our problem is the use of this umbrella term of quality of life. It often actually is used as a synonym for patients' self-report, and it can refer to almost anything that comes from the patient and we call it quality of life.

Symptoms have been on the horizon for many decades as being an important part in the evaluation of cancer therapies, as has functional status. More recently, we've had some theoretical development around needs-based

theories and what this constitutes, and can quality of life be a reflection of what the patient or groups of patients view as being universal needs in relation to their disease and the treatment. I think we saw, even with a very small number of presentations from outside, that this varies widely and it depends very much on the different cancer and also on the different treatments.

But perceptions have been sort of the bedrock of quality of life research in the last 5 to 10 years. We have some problems here because what are symptoms? Symptoms are perceptions, and how does symptoms overlap with quality of life?

Finally, I always like to put opportunity in there because it is a modifier of all of the rest of the self-report. By opportunity, I mean coping strategies, as well as the disadvantages around labeling and all of the opportunity that may be limited or the disadvantage that may be accrued by having the disease or the treatment. We have a big conundrum in that patients come to the disease and the treatment with various abilities that are already pre-established, various function, and various perceptions and differences in symptoms. So, this gives us a problem in that is it an individual phenomenon, and if it is an individual phenomenon, then how would we aggregate across individual definitions that may be specific to individuals?

So, one of the things I wanted to raise, when we do our discussion, is what part of this is an individual and what part of this is a uniform definition? I think Dr. Schilsky and many of us would like to have a single measure that cut across tumor sites and treatments. Let's just throw that out. There may be global assessments that can do that and can compare, but we know that for responsiveness and for sensitivity to change and even for interpretation, we're going to need something that's more specific. The question is how specific.

So, are these things alternative concepts or different concepts? Years ago when I started thinking about health-related quality of life, basically I think it was in response to concerns that patients call quality of life, and then the industry started calling it quality of life. But we've had a perfectly good term that has been around for at least several decades called health status that included death, disease, disability, discomfort, and dissatisfaction. This was known when I came into the field over 30 years ago.

Functional status, or the performance of social roles and activities, is often called quality of life. But function and perceptions are not the same thing. So, two people with the same level of function may have widely different perceptions. So, we have difficulty in relating

that.

Well-being is a concept that is, for example, in the short form, a 36-item instrument, probably the most widely used health status measure across disease categories. It says functional status and well-being. These are feelings of wellness or feelings in general.

Now, the bugaboo is that quality of life has also an equally long history of people outside of the health field to include the environment, adequate housing, income, respect, love, freedom, spirituality, meaning and purpose and the kinds of domains that Carol put on her larger list rather than the traditional World Health Organization driven physical, psychological, and social. I think it's clear that when cancer occurs, many of these broader concerns come into play, and it's a question of whether it's the disease or how the treatment is affecting the entire situation for the individual.

So, we tend to want to work on those aspects of quality of life that are attributed by the patient to health and the importance of health. And Carol has already brought up that how well can this attribution work with different individuals having a different perspective.

These concepts are intertwined, and most aspects of life and life-threatening illness get involved and in some other chronic diseases. So, the broader term

quality of life is in fact relevant in some cases. I think we heard that in the urge for palliative concerns at the end of life.

Patients and clinicians also use language that mixes these concepts: getting up at night to urinate. Getting up at night is function. The urge to go is a symptom. I may concentrate a little bit more on symptoms because that is one of the major concerns of the agency in how is quality of life different from symptoms.

Well, symptoms may be mixed up in I think three major ways. The first I have on the slide here. It may be mixed with signs in the sense that the subjective phenomena may not be seen, heard, or measured. We tend to think of symptoms as primarily things that cannot be observed. That's why it's part of quality. I'm very fond of saying if you can see it, it isn't quality of life.

Symptoms may be mixed up with signs. Symptoms may also be mixed up with functional status, and finally symptoms may be mixed up with well-being. So, if you analyze carefully the concepts that are contained in the instruments, you will see a pretty horrendous mishmash of functional status, symptoms, wellness or well-being, and sometimes quality of life.

This in a sense has done a disservice to the field in the sense that if we want conceptual clarity,

first of all, we need to be distinguishing between health status and quality of life, and both are useful, although different, in distinguishing proximal and distal impacts of treatment in the disease. We should stop calling functional status quality of life or symptoms quality of life or recognize that when we use this label, it is a kit bag of different concepts, but that they are not equal. Therefore, our best chances of sorting out our relationships is to label the concepts carefully. Try to be looking at the domains of instruments around the different concepts and then looking at their relationships. So, if symptoms increase or decrease, how does that affect perceptions of well-being or perceptions of functional status?

This isn't as easy as it might seem in my saying it in that many instruments have been driven by what patients or clinicians say, rightfully so, but the concepts are mixed. But if you look at many of our measures, you will find that there might be five symptoms, two statements of function. They are then aggregated and put into a global score, which means it's almost impossible to sort out what is the relationship, even if we had a theory. If symptoms go up, does functional status change or does wellness change?

So, I would plead that in our analyses that

until we combine concepts, we keep them separate, and that symptoms not be put into functional status instruments or into instruments that are purely quality of life perceptions. And it will be only through the distinctions and through some theoretical driven process.

Now, in my own work, I have this vision that the condition or the treatment changes the patient's disease or the patient's condition. That can be best reflected by a proximal type of measure, such as symptoms. But if symptoms change, you're going to see in many cases a big disconnect between the relationship of the symptom change, to functional status change, or to change in wellness perceptions. In some cases it will be tighter. In some cases it will be looser.

So, our analysis must allow us to be able to do this within a particular tumor or within a particular treatment regimen so that a nausea symptom, for example, which is widespread amongst chemotherapy, can be looked at and the treatments that may change that nausea, which is a perception and vomiting a sign. Then we can look at whether function is, indeed, improved in relation. It's possible that the treatments are not operating through symptoms and may be working simultaneously across the different domains.

I think we have several suggestions of

relationship. It may work far less linearly as symptoms, functional status, perceptions, and opportunities. In fact, the work in the field of disability, through the international classification of impairments, activities, and participation, would say this is not at all linear, but often it is and sometimes it isn't. Identifying those cases will be important.

That's really all I want to say for the discussion.

DR. CELLA: Well, thank you, Dr. Patrick.

We have a number of proposals and challenges set in front of us with those two presentations. I'd like to start us off by asking you to pull out the Points to Consider document that's somewhere in your folders. There are many places we could begin, but let me start by asking you to look at this first page on Points to Consider.

I'd like to be able, in the time that we have allowed, to at least go through Carol's specific proposals that she presented and want to be able to be sure to discuss the implications of Donald's suggested strategy in terms of what that will imply for, shall we say, the dismantling of existing questionnaires and reanalysis, although I don't anticipate we'll get to too much of that today, but I'd like to chart a direction on that particular suggestion of Donald's because it's obviously very key in

terms of giving advice to the agency about how to deal with these questionnaires that come in that have symptoms mixed with functions and mixed with global perceptions. So, we certainly want to return to that. He made a general suggestion and commented that there are lots of details to be worked out. It's not as easy as it sounds.

So, starting with the Points to Consider, this first item, to what extent do disease-related symptoms overlap with health-related quality of life outcomes. I'd like to start with that as a conceptual point, not so much a technical matter at this point in terms of how to deal with existing questionnaires.

I'd like to also subtext this question with Dr. Schilsky's -- as I heard his question, he was asking what's the value added to measuring symptoms. To put it another way, if we measure symptoms well enough, is there any need to measure anything else, and how can we help reviewers of these data, who don't specialize in this kind of data, to understand that there is a need and what that is? So, that's the sort of value-added spin on this more general question about the overlap.

So, I open it up for comment.

DR. DICKERSIN: Could I ask a question for information? I'm worried that some symptoms, or what could be classified as symptoms, fall through the cracks, that

the data actually aren't collected because it's stuff that patients are very concerned about and maybe doctors are less concerned about or the data hasn't been presented in papers before, so it hasn't been brought to the forefront.

I'll just use breast cancer as an example. Patients are very concerned about, when their lymph nodes are removed, the edema in their arms. They're concerned about some of the arm motion problems over the long term because of scar tissue from the dissection of the axilla and menopausal symptoms. These are the kinds of things that aren't typically recorded when you're looking at the side effects of drugs. Yet, they're things that really do have to do with the quality of life if you can't open a car door for your kids as you reach across or whatever.

So, I'm just wondering what about these things that to me seem to fall through the cracks. We may not be collecting data on them, and yet they're very related.

DR. MOINPOUR: David, can I say something to that?

That's one of the values I see for the quality of life questionnaires that exist right now, is that many of them have been developed through a process that involves discussion with not only clinicians but patients in terms of identifying the items that need to be in the questionnaires. So, they are, for that reason, I think

broader than the toxicities that are rated routinely in clinical trials, but that doesn't mean that they still include all of the issues that you may be --

DR. DICKERSIN: I'll give you another example, and I'm not sure if it's a symptom or a quality of life because I just really don't know as much about it. In some of the trials comparing lumpectomy with mastectomy, they looked at women's psychological response, and there's no difference in depression in these women. And yet, clearly there must be. I mean, you talk to women. There absolutely is an effect on women's body image. They have shown that. Where is the middle ground between body image and depression? Is that a symptom or is it quality of life? I don't know.

DR. SCHILSKY: Kay, I think what you're bringing up is several aspects. There are disease-related symptoms, and within that broader category, there are those symptoms that one might expect to be impacted by a treatment or not. So, for example, if one is evaluating a new therapy for breast cancer, one might expect that some symptoms of breast cancer might be improved if the treatment is successful, but lymphedema probably won't be improved because that's related to an anatomical structural defect that is the result of the surgery and probably will not be improved regardless of what other intervention,

unless it's a specific lymphedema directed intervention, but no matter what other intervention for the breast cancer is used, the lymphedema may not improve. I think in consideration of the baseline status of the patients, one has to take into account what could be expected to improve and what might not be expected to improve among the disease-related symptoms.

Then, of course, there are the treatment-related symptoms that we commonly refer to as side effects. So, that's a separate category.

DR. DICKERSIN: That's lymphedema. It's not a disease-related.

DR. SCHILSKY: Yes. Well, but again, I'm trying to keep this in the context of what this subcommittee is trying to do. ODAC evaluates drugs, and I think in the context of evaluating new drug applications, we have to think about what are the symptoms of the disease that could be improved by a therapy, what are the side effects of the treatment that result from the therapy, and then there are the other aspects of the patient's functional status or quality of life that you might not expect to be improved regardless of the specific therapy that's being employed.

DR. CELLA: Stacy.

DR. NERENSTONE: I think we sort of have to

start somewhere, and I think the clinicians' discomfort with quality of life in general is because it is, by its very nature, unmeasurable. But I do think you have to start somewhere, and I think starting with symptoms is going to be important. But I also think you have to, if you relate back to what Dr. Patrick was saying, look at signs. So, it's not only nausea, but if you want a separate scale, you also have to look at vomiting. It's not only pain, but you may want to look at fractures. So, I think you need both the symptoms and the signs to really validate what you have at the beginning and what you have at the end of your treatment because ultimately you're going to have a before and after.

But I also think that it's very important for us to understand the limitations of both symptoms and signs because they can be ameliorated by such a myriad of other things, such as pain control. You're started on a new drug, but you also start on a new pain medication, and your pain gets better. Likewise nausea control, we have many better drugs now and it depends on how aggressive your oncologist may be with those medications.

So, I think we have to start somewhere, and I think that's what we're stuck with. But I think you have to clearly define what you're looking at and you also have to define the ancillary medications that may be used and

impact on these, as well as your study medication.

DR. CELLA: Donald.

DR. PATRICK: I'll try to think on my feet here just for a minute.

I think that's very useful, Stacy.

The issue might come up and let me try to spin an example. Urinary incontinence is one that I know well, and since that was brought up with prostate cancer.

We will have actual signs of leakage that can be seen and actually, some might say, can be measured through pad tests or whatever. There is the symptom, which would be the perception that I need to void. There will be functional status impacts in that I do not go outside unless there's a toilet nearby, a classic item that's been around forever. Then finally, there might be something in the needs-based model that is a perception that would be I have to be careful with what I drink because of my leakage in terms of a needs-based driven type of a model. All of these might be influenced by treatment.

I sometimes feel we're in danger of the proximal/distal -- assuming this is linear. But when we're evaluating a new medication, we would love it if it impacted all of those things and if we got a consistent, well, gee, I don't have to be so careful about what I drink. I can go out without worrying I'm going to have an

accident. I don't have as much of an urgency with my voiding, and my actual incontinence episodes are reduced. Now, that would be the bang-up treatment.

So, I want to respond if you only did symptoms, you wouldn't get all of those other impacts. Now, the symptoms I think are very important to patients, but so is all of the restriction on their life and their ability to live with the condition and with the effects of the treatment. So, you're just simply not going to capture what's important to patients by only concentrating on symptoms.

DR. CELLA: Well, I think we need to clarify something here, and my clarification may reflect, just as your input has reflected, a perspective, and that's always a risk. A different perspective, which is that when we're talking in this venue about symptoms versus quality of life, I don't think that at large we're talking about the distinctions that you've just laid out, which I think are useful and important illustrations. I think we're talking about a community that tends to view all of that that you just laid out as kind of in the symptom domain. That is to say, that if the FDA received an application that had an index that listed 10 items that had the 5 you just went through plus 5 others relating to incontinence, they would perceive that as an incontinence symptom index. They would

be comfortable labeling that. I'm not saying one is right or wrong, but they would be comfortable labeling it as such.

The question they're asking, as I understand it, is not should all those things be measured, because I think that that's a given, and I may be jumping the gun there. But the question is what about perceptions of your family life and your level of depression and other kinds of things that might not be incontinence specific in that setting.

So, even this discussion here illustrates the Venn diagram complexity of definitions. So, I completely agree with you that we need some clarity and I think this group needs to move to some kind of a clarity.

DR. PATRICK: But you're making a distinction just between disease-specific and generic here in that last comment. I did not understand that we were talking about that, quality of life as generic.

DR. CELLA: What I'm trying to say is that the level of discussion that you're introducing is still within an arena -- correct me if I'm wrong, but I believe that the FDA and the ODAC membership would sort of comfortably view as incontinence symptoms and incontinence symptom-related problems and would be comfortable with a total score on a 10-item index that asked people about their perceptions,

their functional limitations because of incontinence, the actual measure of incontinence. There's a comfort level there.

DR. PATRICK: So, they're calling functional status symptoms.

DR. CELLA: What I'm trying to do is lay out the challenge here which is to reach beyond that. I think we need to deal with what you've suggested, Donald, in your discussion which is what your illustration kind of helps us with an example through. But at this level, this first level, we're really talking about what about the things that are outside of the disease-specific or treatment-specific problems.

DR. PAZDUR: If I can just make a point. I think what you're saying is excellent, but I'd like to make a comment. We have to walk before we run a marathon here. And I'd like to emphasize do we even know really, when we talk about symptoms, say, for a common disease such as lung cancer or colon cancer, specifically what symptoms we're even talking about. How well have those symptoms been defined? We've had years of clinical practice. We know how drugs affect tumors in terms of response rates, but if somebody asked, Rich, if you gave 5-FU to a patient with colon cancer, what is the symptomatic benefit of that drug, even though that drug has been around for 40 years, one

could not answer that question.

So, even when we take a look at what symptoms a disease has, I think there's a lot of confusion about that. We have some kind of vague idea that we could patch together, but what percentage this occurs in a patient as they progress during their course of disease I don't think is well defined.

I really applaud you for your efforts, but this is an effort that needs to walk and then do a marathon.

DR. SCHILSKY: Just a follow-up to that, Rick, I think as most people are aware, one of the conundrums we face in evaluating symptoms or relief of symptoms is that the way the eligibility criteria for many clinical trials are structured skews the patient population towards those who are asymptomatic or minimally symptomatic to even be an eligible participant in the trial. So, frequently we'll find that the great majority of the patients enrolled in the trial have no symptoms, otherwise they wouldn't be eligible for the trial. And therefore, it's almost impossible to assess symptomatic relief.

DR. PAZDUR: And the corollary to that is when patients come off of trials, because they do enter with performance status 0 or 1, they're usually coming off because of radiographic progression rather than symptomatic progression. So, this whole issue and how we grapple with

symptoms when patients are entering trials with excellent performance status and relatively asymptomatic and then asking us what is the clinical benefit of a drug -- but I just wanted to address the problem even with symptoms.

DR. CELLA: Right. These issues here are important. They're in the original introductory document that Dr. Beitz put together about whether we should recommend enriching trials, for example, with symptomatic patients and how to deal with these endpoints when they're asymptomatic patients primarily. But I think most optimistically that's an afternoon discussion and maybe even a June discussion or an interim discussion.

Jody, you had your hand up a while back.

DR. PELUSI: Yes. As this discussion progresses, I don't want us to forget also the cultural issues because, as we start to look at symptoms -- and let's take the example of Ms. Simper when she was talking about pain in pancreatic cancer. What we see at ODAC is a slide that says pain, and my question becomes, do we just ask people if they have pain? In the setting where I work, I can't even use the word pain. It's not even appropriate to ask. I have to ask about are you able to be a wife, are you able to do your daily work. So, I think even the symptoms sometimes that we get at and the definitions, we have to really look at the cultural implications of how

we're asking those questions and collecting that data as well.

So, if we can just remember that because I think one of our biggest issues is trying to recruit more minorities, more under-served people into our clinical trials, and this is going to become another issue. While we're looking at this, I think we better start to look at that as well as we accrue more people.

DR. CELLA: Could you let us know where you work to give us a context for your comment about not being able to ask directly about pain?

DR. PELUSI: I'm from Arizona and I do rural clinics for people who don't have access to our metropolitan areas in the oncology realm.

DR. CELLA: Thank you.

Carol.

DR. MOINPOUR: I wanted to clarify one point about my proposal on not measuring just symptoms, but also providing some data for the broader health-related quality of life domains. I'm not proposing that an application would need to show effect in all those areas, but just that the information is very important for evaluating even the symptom data to know what happens in the other areas, the broader areas of quality of life. So, because we don't have a large database in this field, we may learn that in

fact symptoms really aren't particularly affected by a new drug, but that maybe emotional functioning or physical functioning is affected.

So, it's really providing the information so that we can have a more thorough evaluation of the effects of the treatment and indicating where we see improvement and where we don't or where we see deterioration in the case of treatment-related side effects. But I wasn't suggesting that all those areas had to show an effect of treatment.

DR. CELLA: Jeff.

DR. SLOAN: I just wanted to return back to the question that you posed, David, in terms to what extent do disease-related symptoms overlap with health-related quality of life outcomes. It seems, as I think we're all wrestling here to a certain extent with the subject matter, part of the issue I think here is we're trying to explain the complexity of human endeavor in a very simple and almost a taxonomic way, and that's very difficult.

If we go back to that bowel function example, for example, when we studied bowel function in a recent trial, there were all of those aspects in terms of -- the number of stools, of course, is the gold standard. We all know that, as we heard this morning by the patient advocates in particular, the number of stools is not

necessarily the most important outcome, and having to get up at night is not necessarily the most important outcome. It's whether or not the patient is perceiving that as a problem. A lot of folks get up during the night, bring in the cat, take out the cat, whatever because this is just part of their daily routine.

However, I think what you're talking about in particular, David, is separate to talk about quality of life as the other aspects of is this disease or treatment impacting things beyond basic symptomatology so that we can say my quality of life is actually affected as well. Yes, I'm having problems actually because I have to get up at night six times and I'm not getting any sleep and it's messing up my day. Maybe that's the aspect that we're talking about.

But in saying that, then I think the answer to that question, long-winded though it may be, is a simple yes, in that they are irreparably intertwined. And I'm not sure that separating these things is really achievable as much as just identifying my perspective, which I'll throw out, that one of the problems in terms of quality of life is that it has become a gestalt umbrella concept, and I think for most folks, certainly from what I heard from the patients this morning and their representatives, was the patient perspective is that quality of life is a gestalt

thing and that we can measure symptoms and these others. And it's important, in terms of definitional, to recognize whether it's a separate thing from functional status and these others or it's just part of the overall umbrella. I'm not sure what the answer is, but perhaps that's a place to start to decide which one of those things it is.

DR. CELLA: Dr. Williams?

DR. WILLIAMS: From a reviewer's perspective, you might keep in mind the kind of questions that arise when we're evaluating these scales. I think very important to us would be when do these rise to the trustability that we would put them in the label or when would they be a primary endpoint. Are they in such a form that we could describe them and express to the patient what they mean?

Some of the discussion sounds like these are investigative tools or maybe they'll lead to further investigations and we'll maybe focus on what's causing this change in global score. But I think at this point in time one of the frustrations is really not knowing what to do with all this data and should you put it in the label. So, we're a little more comfortable with putting symptoms because we know what that means and we can express them. But how to express a change in a global score from five different scales that's been summed together and there's a delta of 2, that's a real problem for us.

DR. CELLA: Any other comments? Donald.

DR. PATRICK: I still think we're making a mistake if we confound the type of instrument with the concept. Global sounds to me like you're talking about it as generic, and I could see evaluating a drug without a single generic instrument involved. So, I don't believe that condition-specific instruments should be labeled symptom indexes. I don't quite understand why that is the issue. If we're meaning global as how does it affect your ability to work, not attributed to the condition or its treatment, I mean these concepts run across within disease-specific and in generic instruments.

So, I'm not quite clear on the question. Is the question should we be evaluating drugs using non-condition-specific instruments?

DR. CELLA: The question has nothing to do with the instruments yet. I'm trying to just get a general conceptual sense of a possible consensus or where the committee is. It's not instrument related right now.

DR. PATRICK: Well, when you say that they consider I don't go outside unless there's a toilet nearby as a symptom --

DR. CELLA: No. What I was saying was that I believe that when it comes to the reviewer, the non-expert reviewer, if you will, which is where ODAC has told us they

are -- Dr. Schilsky acknowledged that there are no quality of life experts on the committee, and yet they look at these data. They're people who know statistics and who know medicine and oncology, but all the different questionnaires are a confusing morass.

What I was trying to point out was that your definition of symptoms is narrower than theirs. We may need to deal with that first, but I was just trying to say that the outside observer's definition of what would be called a symptom is I believe broader than your presentation suggests that yours is. And you may be right. It's not a debate about what's right or not.

DR. PATRICK: I just want us to define global because this is very confusing terminology. If we really mean generic, not attributable to the condition --

DR. CELLA: I think in Carol's presentation -- you can speak for yourself, but I believe global was intended to be a single rating of an overall quality of life.

DR. PATRICK: That's how I understand it as well.

DR. WILLIAMS: I don't believe that we've been tied up with the definition of symptom. I think we've looked at individual scales that may have had symptoms and signs or whatever you want to call them and thought that

this appears to be a scale that represents a clinical finding. But I'm not aware that we've had a debate about what a symptom is.

DR. CELLA: I accept that as a given.

Rich.

DR. SCHILSKY: David, I guess a couple of other questions maybe to come back to something I said earlier.

I think where we have a lot of difficulty in ODAC, being mostly clinical oncologists around the table, is most of us are comfortable evaluating symptoms -- call it symptoms and signs, if you wish. Most of us are comfortable evaluating those. Most of us are comfortable evaluating some functional status, what we typically call performance status. Beyond those elements, it's a little bit unclear as to what the value added is of other measures once you get beyond symptom assessment and functional status.

I think the other aspect that we find very confusing is, in a sense, the multiplicity of asking the question. In other words, do we really need 10 ways of asking people if they're incontinent? Can we ask it one way or two ways? And if you ask it 10 ways, which of the 10 is the most reliable indicator of whether they're actually incontinent? So, that's where things get very confusing to people on the committee.

DR. CELLA: Well, embedded in this discussion, there are two positions on the table. I'd like to lay them out and get a reaction, and it's not even necessary to say whose they are because I might not state them right. So, I can assume them as mine if others think that that's not really what their position is.

One position is that there are certain circumstances in which a good symptom profile, however defined, is enough data to receive. Another position is that if that's all you measure, if that's all you receive, then you may miss important problems that aren't being measured by the symptom profile.

We don't need to necessarily take a position one way or the other, but these perspectives have at least been hinted at, one more or less formally presented by Carol. One of them is that, okay, if you only measure symptoms, then you may miss something and we can detail what that is. The other is that there are circumstances in which a submission of data that is symptom focused, in fact, exclusively symptom focused, is in certain circumstances adequate and appropriate. Can we get some discussion about that?

DR. PAZDUR: Do you want to define symptom?

DR. CELLA: That's been a little bit difficult. Well, I'll try again.

Carol.

DR. MOINPOUR: Well, that's a good question and I was going to mention that just a few minutes ago. I believe we do have to make this distinction between disease and treatment-related symptoms. I would even say that we should ask an applicant to provide data on those disease-related symptoms that are currently known in the literature to be associated with a particular site of cancer, and then maybe that would mean, in terms of disease-related symptoms, where the new drug is supposed to alleviate them, that there would have to be a requirement for a sufficient number of patients who are symptomatic.

But then the second area -- and this is where people may not have as much prior information to know -- would be the treatment-related symptoms, and that there should always be a set of items that deal with, as best can be identified, what the treatment toxicities are associated with that particular agent. There we'd be looking for harm.

Then what to me is of value then of the other domains of quality of life is you see how far the harm or the improvement extends from the symptom area.

DR. CELLA: Dr. Dickersin.

DR. DICKERSIN: This probably shows how little I know about all this. But I actually was hearing the

position slightly differently, which is that maybe -- and I could have this wrong -- what ODAC wants is information to some extent about the symptoms and how to interpret symptoms. Yet, the people working in the quality of life field actually have a more sophisticated, detailed -- whatever the right word is -- way of looking at this that really goes well beyond symptoms into a different definition of quality of life.

So, maybe it's very good that we're all working together so that ODAC is being informed -- I'm sure being informed and this is very helpful to me as a trialist actually using quality of life outcomes -- how they should be separated. Everything I'm hearing just rings such a bell, and yet I might have, in the beginning, joined symptoms and quality of life myself. I'm still worried about things falling through the cracks. But maybe it's not that we're coming from two separate places, but that there's a lot of education that's going on.

DR. SCHILSKY: I would just say my own view of sort of the purpose and the role of this subcommittee should be to remain focused on the issues that will be valuable to FDA, ODAC, and the investigator community in the design of clinical trials that will ultimately support the approval of a new drug. I don't feel that the purpose of this committee should be a broad discussion of

validation of the whole field of quality of life research. That's much broader than I view the mission of this committee.

From the ODAC perspective, I think Carol's suggestion is outstanding. I think that the committee would feel very comfortable with receiving data that says, okay, for this disease and this population of patients, these are the five most common symptoms that commonly occur related to the disease, and here's documentation as to what happens to those symptoms over time during treatment. Here are the 5 or 10 most common side effects known to be associated with the therapy, and here's documentation of what happens and how frequent those symptoms are over the course of therapy. I think if we had information like that provided completely and unambiguously, it would be enormously valuable to the committee.

DR. CELLA: Lillian.

DR. NAIL: I wanted to take perhaps an ill-considered shot at putting the two positions closer together. It's very clear that the largest variance in function and emotional distress is driven by symptoms, and those may be symptoms of the illness, a combination of side effects of different treatments. And the example Diane gave is an excellent one where we have women with breast cancer, problems with strange sensations in the arm,

functional limitations in the arm, which is the downstream of arm problems. But they're getting other treatments that cause other problems that are going to vacillate along the treatment continuum.

However, Diane's original question, do we know what all the symptoms are, part of the unaccounted variance in changes in function and distress is probably due to symptoms we haven't recognized. That's one reason why it's important to look at some of the other indicators. The symptoms we've identified alone won't do it.

There are several good examples, but one of the most recent ones is cognitive changes that are really affecting people in the work domain and because we haven't consistently asked about it, we've missed that entire domain. So, we really have to have that other piece.

The other thing is there are things that you can do to improve quality of life that are not directed at symptom management, and those influence the symptom appraisal process and helping people have an accurate cognitive schema about what those side effects and symptoms are so that they can plan their life around it. So, there's another piece of the variance that could be explained by inaccurate or unfortunate appraisal processes and lack of information ahead of time. So, I think we need to look at it as looking at symptoms, looking at the

impact, and recognizing that we don't know everything about what drives impact.

DR. CELLA: It's 10 o'clock. I don't want to quit immediately, but I do want to close down so we can take a break and remain on schedule. Are there any other comments that people have? Carol?

DR. MOINPOUR: I'd want to make one more comment.

I feel very strongly about the need for the domains, additional to symptoms, just based on an experience in one trial that we did where symptoms were not associated with a very significant effect on emotional functioning, and when we looked at the patients who were symptomatic, this was not the explanation for deterioration in emotional functioning. Yet, this finding, as strange as it was and not directly hypothesized by us in our protocol, was consistent with clinicians' experiences on a small scale. So, it did not seem that strange to clinicians looking at the data.

So, there's a case where symptoms really weren't necessarily affected in the trial, but one of the broader domains of health-related quality of life, in this case emotional functioning, was. So, if we would not have measured that, we would have missed that whole effect. So, I just think that's why I feel very strongly about the

comprehensiveness of the assessment, keeping it reasonable to health-related and restricted to areas affected by treatment.

DR. CELLA: Thank you, Carol.

I would like to spend a couple of minutes seeing if there is comfort, agreement on a few basic points that tie in Carol's presentation, Donald's presentation, and the discussion.

I'll start with Carol's first proposal actually which is that the expert regarding what she termed patient benefit is the patient. Is there a sufficient comfort level to -- is there anyone that would be uncomfortable with that position?

(No response.)

DR. CELLA: Part of this is just wanting to close with some good, solid consensus and to give me a sound bite for the end of the meeting.

(Laughter.)

DR. CELLA: The expert is the patient. This is a nice thing we can close with.

Although I'd like to get a little bit more of a stretch here. No single measure will emerge. That doesn't mean that we don't have a responsibility here to simplify and codify in a coherent way for the FDA and for ODAC how to deal with all these data. Is it obvious to all of us

that, given the complexity of this issue and the need for responsiveness, as Donald pointed out, that we know already that there's not going to be a single, one-size-fits-all approach?

(No response.)

DR. CELLA: So, we know a couple things.

Finally -- and this is one if there's any discomfort, because we haven't clearly defined the term and we need time to do that, but that symptoms are a reasonable place to start and even to focus, in some circumstances, one's primary analysis. Discomfort with that?

These are three sort of general concluding points that at least get us started. There's a lot of work to be done that we will engage Carol and Donald and others in.

DR. PATRICK: I just would urge you not to neglect the last part of Carol's statement in that you need to look at the symptoms that are both benefits and harms down the line and the advantage that there will be cases in which functional status may be affected where symptoms are not. That's useful information in evaluating the medicine. So, I agree, David, but it's not all in the symptoms. It's a useful place to start, but it isn't everything.

DR. MOINPOUR: I just wasn't quite comfortable because that is all you talked about in that last

statement, just symptoms.

DR. CELLA: Yes. That's why I tried to say start and focus a primary analysis plan. But I was trying to come short with a simple statement to come short of saying that it's enough to look at completely. I'm not trying to steer away from that, but I will modify that, not now, because I think we need to take a break. I'll bring it back.

DR. SLOAN: David, would it be fair to say that symptoms are a necessary part but not a sufficient, complete in a QOL investigation, let's say, or answering the QOL component of the trial?

DR. CELLA: Actually that reminds me, Jeff, of the whole issue of QOL. I didn't mean to -- and I can see that I did -- imply that that would be considered a quality of life submission. That's an important labeling issue and I'd like to be really clear that if somebody went that way, it probably would not be, based upon Carol's presentation, Donald's endorsement, and the parent committee position, a quality of life submission. So, that brings up a different issue. Carol wisely selected patient benefit on that first proposal to avoid perhaps that conceptual issue.

I think we'll take a break and call that enough for this session. We'll obviously revisit some of these issues. Thanks.

(Recess.)

DR. CELLA: Now we move to the session on clinical significance and clinical interpretation so we'll be able to interpret the information that we made so very clear in the last session.

(Laughter.)

DR. CELLA: Dr. Jeff Sloan from the Mayo Clinic is going to present, and Jeff, if you could be sure to talk into the microphone and try to not turn your head too much, then we will pick you up better on the audio.

DR. SLOAN: Well, first of all, I want to thank David for inviting me to stick my neck out here. I'll be looking for him to save it if I get into too much trouble.

I think everything even we've talked about this morning seems to underline this idea of clinical significance in the comments, particularly from the folks from NIH are saying. So, what does it mean? I think that's a question that I've heard more than I care to, but it is probably the most unnerving question with respect to quality of life measurement.

I'm going to throw out, as Carol did earlier, some ideas, some proposals, which hopefully will be points of discussion as opposed to, yes, this is what I absolutely think we should do and this is the only way we should go. But hopefully these will be useful suggestions.

One way to start this is we say, okay, why is this so difficult? Perhaps this is obvious, but I thought it was worth some recapitulation, at least a little bit at the beginning. As people said, it is an intangible construct for the most part, and in some ways can be thought of as a gestalt, multi-dimensional entity within the psychosocial realm of how are you doing basically. We can all say how we're doing in general, but exactly how do you tangibly and quantitatively measure that?

There is an analogy that I wanted to bring to bear here, which may or may not have great relevance. Hopefully it does, otherwise I wouldn't have included it. But 100 years ago, the blood pressure cuff was being tested in a not dissimilar fashion the way we're talking about assessing tools for measuring quality of life instrumentation today. The clinical significance of what scores meant, what those anomalous blood pressure scores, the numerator and denominator, systolic and diastolic, what do these things mean was not known, which is kind of an interesting shift in time to think about.

One of the questions facing folks at that time was what do we use as a gold standard. How do we know that a shift in blood pressure is clinically significant? At that point in time, they figured it was important to tie it to a clinical outcome. Yes, it is 100 years ago. It was

thought that massage therapy was the gold standard in terms of assessing for, let's say, clinically impacting blood pressure. It was a known or a given, assumed, that if you gave people a massage and it was more, let's say, regularly or routinely accepted, especially in Britain, that M.D.s would administer massage therapy on a regular basis, and they were the only people that should be administering massage therapy because, my goodness, these are clinicians. This is an important treatment to be given. Interesting how times have changed. But massage therapy was used as the gold standard to assess whether or not you could pick up changes by the blood pressure cuff and the scores changing.

Now, the present guidelines for -- that should be BP, not BO. I apologize for the typo.

(Laughter.)

DR. SLOAN: I mean, there are guidelines for the clinical significance of BO, I'm sure.

(Laughter.)

DR. SLOAN: If nothing else, David, I'll inject some humor into the morning. You always have to have somebody for comic relief. Right?

But the key question is, as we discuss what is a clinically important shift in quality of life measures, can we all say we know definitively what a clinically

significant shift in blood pressure scores is in all settings across all situations for all patients? I think the answer to that is still, 100 years later, it is still open to discussion to a certain degree.

We know a lot more about blood pressure scores now than we did 100 years ago, but if we can assume then it takes 100 years to figure something as simple as blood pressure scores' clinical significance, then maybe we need to keep in mind that it's going to not necessarily be achievable to know all things about every aspect of quality of life in terms of the clinical significance. But we have to do something.

Well, the first thing I'd like to point out, hopefully as David requested, sticking my neck out, as a statistician, I guess I'd like to stomp my foot a little bit and talk about, first of all, what I believe that clinical significance is not. In some ways defining things by saying what it is not can help.

One thing it is not is statistical significance and is often linked to clinical significance. Just because you got a p value that is less than .05 doesn't mean that you have a clinically significant outcome, and maybe that's obvious. But to bring that home, I'd like to use another example.

In a particular study we did recently, we had

the health status questionnaire, which is a rather lengthy questionnaire dealing with all aspects of quality of life, before and after scores on 1,300 people. In presenting the data to our clinical folks, the discussion centered around the idea of, wow, look at all those significant p values. Yes, they're all statistically significant p values. They're all less than .0001 because we've got 1,300 folks. So, we could distinguish between a score of 12 and 13 on every domain, translated onto a 0 to 100 scale. That doesn't mean that a person's or a group's health status really changed to such a degree that is clinically significant.

It's the conundrum within the statistical world, if you will, more observations is good, the bigger sample size, the better, to a point. With 1,300 folks we can prove just about anything is statistically significant. Without a priori determination of what we're going to say is an important clinical outcome, a clinically significant outcome, p values are totally meaningless. I think too often a statistical significance is actually used as the benchmark. Well, it must be good because p is less than .05. And hopefully, we will go beyond that.

One way of attacking this is to look at a general classification system for methods that are assessing clinical significance. There are a number of

ways that I think in the literature -- as Donald had mentioned earlier, this stuff has been around for a little while. So, the idea of assessing clinical significance is not new. So, we can talk, however, about, in terms of an FDA, let's say, submission, categorizing the type of clinical significance or the method for assessing clinical significance that can be put into some very broad categories.

If the world were perfect, every tool developer would be able to specify a shift of X units on my tool is clinically significant. Some tool developers have done some good work in that area and made some recommendations. That's one way, I think, of assessing clinical significance, and if we can assume that the tool developer took a sound scientific and measured experiential trajectory in developing the instrumentation, then that's not an unreasonable way of saying a priori the tool developer says the shift of 5 units is clinically important for groups in my assessment tool. We can believe that.

Another way, I think which is probably the most common way, is investigator defined. What I've got here are all the acronyms for the various methods. I won't go into any detail. I will just list them briefly. Yes, there's the effect size approach, looking at how many standard deviations apart the scores have moved; the

standard error of measurement, looking at a similar related effect to the effect size only in terms of talking about the standard error rather than standard deviations; the ERES, or empirical rule effect size. This is a method that we kind of pulled together over the years in relation to some other people's work as well, the idea being can we talk about effect sizes as being -- as changes of being small, medium, or large in a general classification taxonomy like that. And then R squared, talking about the idea of if a certain amount of the variance is accounted for by a particular instrument, then this must be a clinically significant shift in terms of a prognostic variables approach. All of these need to be defined by the investigator, though, ahead of the game, a priori.

There is also some other work in this area in terms of classification of clinical significance, a posteriori methods asking the patient after the fact has your quality of life changed a significant amount or not. The most commonly recognized issues here or approaches, I should say, are the MCID, minimally clinically important difference, and minimal important difference, the work of Drs. Jaeschke and Osoba up in Canada, where we basically say, okay, the QOL scores changed. What were the changes in the QOL scores for people who told us after the fact that, yes, my quality of life changed substantially, and

then taking an average value, for example, and saying that represents then a clinically observable or the patients can perceive that size of a difference.

The fourth method, as I mentioned, which is more common, I just want to throw it out again to reemphasize that this is probably the weakest approach where people happen to find parsimoniously a significant p value and a posteriori say, ah, QOL has changed because we have a significant p value. Again, people do this, so I had to figure this is one classification, if you will.

And then a fifth way we see oftentimes, which again I want to raise as a little bit of a straw man per se, where we anchor the quality of life scores to a clinical outcome. For example, we ask people about their ability to walk and so on and then ask them about their quality of life. Well, to me there's a little bit of circularity there, a little bit of redundancy. If what we want to look at is a person's ability to walk and what we think that the drug will impact is their ability to walk, then asking them about their quality of life as well as a surrogate endpoint may be redundant.

There are three subtopics that I want to deal with relatively briefly in which every one of these five approaches can be applied.

Typically we want to talk about comparing

groups. What is a meaningful change in group comparison? This is often done by looking at just simple summary statistics such as means and medians and the usual t-test and Wilcoxon procedures there. That's probably the gold standard right now. Whether it's an acceptable gold standard or not I think is open to discussion, but that's basically what people are doing and probably what folks are seeing in terms of application.

Some other things that I think can be thrown into this approach as well is to actually look at the difference in the proportion of patients that achieve a particular endpoint, the proportion of patients who actually are, for example, no longer depressed as a result of some administration of a treatment, no longer experiencing neuropathy.

As well, there are for some scales, for example, the well-known symptom distress scale, which has been around for quite a while by McCorkle and Young. They defined a priori through their work that a score on the scale of greater than 30 would indicate that a patient was experiencing sufficient or substantial, I should say, symptom distress and so just looking at what proportion of patients are by that definition actually distressed.

Another way we can look at things is talking about the difference in regression coefficients. That's

often done as well. We've got some statistical issues there, not the least of which over time, whether a change in slope is actually representative of individual patients, which is a segue into the next aspect of discussing clinically significant change, talking about, okay, how do we look at an individual patient and say, yes, their quality of life has changed on some particular domain.

Again, this is where I think the tool developers can be a great help in terms of the most well-developed tools will have norms, certain percentiles and percentages that may be applied, and if a priori an investigator can define a clinically significant shift as a shift in the norm of a certain amount because this represents a shifting of the overall population, then that seems a reasonable way to go.

The number of categories that a score shifts on an individual item is also another way of looking at individual comparison, again a priori defined by the investigator. How many folks have actually shifted from mild to moderate? How many folks have actually shifted from moderate to severe? If a person sees a one-category shift, is that clinically important? And defining it in a very simplistic way I think will help to intrinsically include a meaningful clinical significance in that approach.

Another way of doing it is a more statistical approach where you look at, for every group comparison method, there are ways of adjusting the results for group comparison methods down to individual methods. Jacob Cohen is I guess the first person that I can think of that wrote this a long time ago talking about the root 2 approach where he showed that you can adjust the power estimates for the two sample t-tests to a paired comparisons experiment just by multiplying all the power estimates by the square root of 2. That doesn't apply in general, of course, but it gives you the flavor of the idea of, yes, we could actually statistically just say, well, let's take what's good for the groups and adjust that accordingly using that statistical rule. I'm not sure how palatable that is in a generic situation, but it is one possibility.

Finally, I think perhaps this is the most important aspect for clinicians in particular. Okay, I have a patient. I give them a 30-item QOL questionnaire. I see a whole bunch of numbers that I have from before and what they have now. What actually should I do, could I do, would I do if I observed changes in this patient? What is going to be the clinical trigger for me?

Again, I think this has to rest in the hands of the clinicians rather than the QOL investigators in terms of if they can a priori, in consultation with QOL

investigators, say, okay, this is going to be clinically important. This would cause me to intervene with a patient.

For example, taking the functional living index of cancer example, this was basically the rationale behind its early development. The idea was it was to serve as a mechanism for clinic referral where each one of the 22 items in the FLIC was intended as a clinical trigger. Take, for example, there's one question that asks how much are you thinking about your cancer, from not at all to all the time. And if people were scoring anywhere from 5 to 7 on that 0 to 7-point scale, we would say that was indicative that a clinical referral to psychological or sociological interventions need to be considered at least. That was the intent.

As you can imagine, though, that is not a simple thing, and I think a lot of work needs to be done in that particular area. Again, it has to be a collaborative process between clinicians and QOL developers.

One other thing that I did want to mention that I have seen -- and it's not a new idea at all, and it seems to becoming standard in the literature, and I think that might be something that we could perhaps recommend as a committee -- is that all of these things, if we can assume, do have some sort of dimensional component to them and we

can identify the dimensional component which each particular tool is defined, then we should be able to talk about things on a 0 to 100 dimension, if you will, and allow for an easy interpretability both for clinicians' understanding and for interpretability across domains.

In terms of clinical significance, I want to throw out another idea. This one I'm probably going to get chewed over the most for, but that's okay. As I mentioned, I'll blame David for it. So, that's fine.

Some of the work that we've been doing in looking at clinical significance really, in bringing together all of the literature, is trying to equate the methods. What is both interesting, puzzling, but very satisfying and almost comforting is to see that all the methods of approaching clinical significance kind of say the same thing. They will vary slightly in terms of the absolute number of points or way in which these scores may be interpreted as changing, but as a general rule of thumb, if a set of scores have changed by a half a standard deviation, then that, throughout all the different ways of approaching things, is really a minimally required shift for people to say, we have something, we have seen something, independent of sample size, independent of the tool or the dimension being looked upon.

Perhaps this is too simplistic, but at least

it's kind of saying, well, if it moves this much, all right, I'm going to believe it. Then there's something here. We don't know if it moved this much, but if we saw it move this much. We saw the elephant, so it's definitely not a duck. It's bigger than a duck.

Now, if this again an unpalatable approach for things, protocol-specific modifications, and I think as Dr. Schilsky mentioned, justified from data and documented evidence can easily be applied to this, whereby we say, maybe here we can allow for a little bit more precision, so a quarter standard deviation is going to be a shift or, alternatively, three-quarters.

Is this too simplistic? I don't know. I'm kind of simpleminded, so I kind of like it.

Another way to talk about these things is, okay, if we don't like this hard and fast half a standard deviation is the most important, I think what is appealing, certainly to the clinical colleagues with whom I've dealt over the years, this idea talking about small, medium, large. Just like talking about pain, it's hard to define, but we all know what it is.

There was some very good work done on a well-established tool, the Cleeland brief pain inventory measured on a scale from 0 to 10, which demonstrated that anything from 0 to 3 was basically very little pain.

Anything from 4 to 6 was moderate pain or the patient was saying, I could use some help here. And anything more than 6, from 7 to 10, on that scale was I'm out of control. I really need some pain medication.

So, it boils down to again this classification of the worm, the duck, the elephant. If we can identify differences between the worm, the duck, and the elephant, then -- isn't this a wonderfully intellectual conversation?

(Laughter.)

DR. SLOAN: At least if we can see those things and people can understand things in that terminology, worm, duck, and elephant, I think that will, hopefully, bring the discussion down to a level where clinicians and the lay public will feel comfortable talking about this thing because I do firmly believe that patients can tell, just as in that pain example, which was validated psychometrically in a very sound, scientific manner, that if you ask a patient is your pain the size of a worm, a duck, or an elephant, they can tell you. The clinical implications for a patient having pain the size of a worm or a duck or an elephant are obvious to clinicians. They know how to deal with those things.

I always end any discussion of quality of life with the most important aspect. I think it was brought through this morning in terms of clinical significance.