UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

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CHEMOPREVENTION OF COLORECTAL CANCER

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MEETING

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TUESDAY,

MARCH 19, 2002

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The Advisory Committee was called to order at 8:00 a.m., in the Kennedy Room of the Holiday Inn, 8777 Georgia Avenue, Silver Spring, Maryland, by **Dr. M. Michael Wolfe**, Chairman, presiding.

PRESENT:

DR. M. MICHAEL WOLFE	Chairman
DR. JOHN A. BARON	Guest Expert
DR. MICHAEL CAMILLERI	Member
MS. SUSAN COHEN	Consumer Representative
DR. BYRON CRYER	Member
DR. RONALD P. FOGEL	Member
DR. CURT D. FURBERG	Consultant
DR. NANCY L. GELLER	Member
DR. GEORGE S. GOLDSTEIN	Industry Representative
DR. BARNETT KRAMER	Guest Expert
DR. ALEX KRIST	Guest Expert

PRESENT: (CONT.)

DR. JOHN T. LAMONT	Member
DR. BERNARD LEVIN	Guest Expert
DR. ROBERT A. LEVINE	Member
DR. DAVID A. LIEBERMAN	Guest Expert
DR. SCOTT LIPPMAN	Consultant
DR. DAVID C. METZ	Member
DR. DAVID F. RANSOHOFF	Member
DR. JOEL RICHTER	Member
DR. ANIL K. RUSTGI	Guest Expert
DR. MARIA H. SJOGREN	Member
DR. TOM PEREZ	Executive Secretary

C-O-N-T-E-N-T-S

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P-R-O-C-E-E-D-I-N-G-S

(8:11 a.m.)

CHAIRMAN WOLFE: Good morning everyone. I would like to get the meeting started. I am Michael Wolfe, and I am the Chair of this advisory committee for the FDA, and before we get started, I wanted to just briefly make a couple of comments about this meeting.

This meeting is a little difference than certainly some of the ones that I have attended, in that we are not really discussing any specific agent. Rather, we are discussing general policy regarding trying to provide guidance for the FDA for future studies that will look at chemoprevention for colorectal cancer.

We will have speakers this morning discussing the problem of pathophysiology and other aspects, and we will be having different representatives from the public speaking as well, and we will also have a discussion in the afternoon to very specific questions to be answered, and to be discussed at great length.

This meeting is a little different than most meetings as I mentioned, but this actually more resembles an NIH consensus meeting, but it is not an

NIH consensus meeting.

It may resemble it, but it is not, and we have to keep that in mind when we go through our discussion.

This is FDA, where the goals are different, although we certainly hope that NCI is represented here, and will help in the future should some specific recommendations be made, and certain studies be done.

Before we get started in the actual meeting, I would like to go around the table and have the people sitting at the table introduce themselves, and we will start with Dr. Houn.

And also before I forget, when you do speak, when all speakers speak, please turn your microphone on, and when you are done, please turn it off to avoid feedback.

DR. HOUN: Thank you, Dr. Wolfe. I am Florence Houn, and I am the Office Director for Drug Evaluation III in which the GI Division is one of the divisions in the office.

DR. RACZKOWSKI: Good morning. I am Victor Raczkowski, and I am the Acting Director of the Division of Gastrointestinal and Coagulation Drug Products.

DR. AVIGAN: Good morning. I am Mark Avigan, and I am a Medical Officer in the same division.

DR. CAMILLERI: Good morning. I am Mike Camilleri, and I am a Professor of Medicine and Physiology at the Mayo Clinic, Rochester, Minnesota.

DR. SJOGREN: I am Maria Sjogren, and I am the head of research at Walter Reed Army Medical Center.

DR. CRYER: I am Bryon Cryer, Associate Professor of Medicine, University of Texas, Southwestern Medical School, in Dallas.

DR. FOGEL: Good morning. I am Ronald Fogel, Division Head of Gastroenterology, Henry Ford Health System.

DR. LAMONT: And I am Tom LaMont, and I am Chief of the Division of Gastroenterology, at Beth Israel Deaconess Medical Center, in Boston.

DR. LEVIN: Good morning. Bernard Levin, Cancer Prevention, M.D. Anderson Cancer Center.

DR. METZ: Good morning. David Metz, Associate Professor of Medicine, Division of Gastroenterology, at the University of Pennsylvania, in Philadelphia.

DR. GELLER: Nancy Geller, and I am the

Director of the Office of Biostatistics Research, at the National Heart, Lung, and Blood Institute.

CHAIRMAN WOLFE: Again, I am Michael Wolfe, and I should mention where I am from. I am a Professor of Medicine and Chief of the Section of Gastroenterology, at Boston University.

DR. PEREZ: Tom Perez, Executive Secretary to the meeting.

DR. RICHTER: I am Joel Richter, Chairman of the Gastroenterology at The Cleveland Clinic.

MS. COHEN: I am Susan Cohen, and I am a consumer member, and I have had a colonoscopy.

MS. ROACH: Nancy Roach, and I am a patient representative and I am a member of the Colon Cancer Alliance.

DR. FURBERG: I am Curt Furberg, and I am a Professor of Public Health Sciences, and I am also a new member of the FDA Subcommittee on Drug Safety and Risk Management.

DR. LIPPMAN: Scott Lippman, Cancer Prevention, M.D. Anderson.

DR. GOLDSTEIN: George Goldstein, Industry Representative, and independent consultant after 25 years in the pharmaceutical industry, and I, too, have had several colonoscopies.

DR. LEVINE: I am Bob Levine, State University of New York, Upstate Medical University, in Syracuse, and Professor of Medicine.

DR. BARON: I am John Baron, Epidemiologist and Internist from Dartmouth Medical School.

DR. KRIST: I am Alex Krist, an Associate Professor at Virginia Commonwealth University, MCV.

DR. RUSTGI: Good morning. I am Anil Rustgi, Chief of Gastroenterology at the University of Pennsylvania.

DR. RANSOHOFF: I am David Ransohoff, a Gastroenterologist and Epidemiologist from the University of North Carolina.

DR. KRAMER: Hello. I am Barry Kramer, and I am the Associate Director for Disease Prevention at the National Institutes of Health, and the Director of the Office of Medical Applications of Research.

DR. LIEBERMAN: And I am David Lieberman, and I am the Chief of Gastroenterology at Oregon Health Sciences University.

CHAIRMAN WOLFE: All right. Thank you. Dr. Raczkowski will begin the discussion now. Oh, I'm sorry, but before Dr. Raczkowski, Tom Perez will give his opening statement.

DR. PEREZ: Good morning. The Food and Drug Administration has prepared general matters waivers for the following special government employees who are participating in today's meeting of the Gastrointestinal Drugs Advisory Committee Meeting being held by the Center for the Drug Evaluation and Research:

Dr. Curt Furberg, Dr. Byron Cryer, Dr. Joel Richter, Dr. Robert Levine, Dr. Scott Lippman, Ms. Nancy Roach.

The waivers permit them to participate in the Committee's discussions and standards, and study designs of clinical trial testing, efficacy, and safety of chemopreventive agents that are being developed to gain FDA approval.

And reducing the risk of sporadic colorectal at the adenomatous polyps, and sporadic colorectal cancer. A copy of these waiver statements may be obtained by obtaining a written request to the FDA's Freedom of Information Office, located in Room 12830 of the Parklawn Building.

In addition, we would like to disclose that Dr. David Metz, Dr. Ronald Fogel, and Ms. Susan Cohen, have reported interests that are exempt pursuant to 18 U.S.C. 208(B)(2).

Dr. Michael Camilleri, Dr. Maria Sjogren, and Dr. Michael Wolfe did not require a general matters waiver because it has been determined by the agency that they have no financial interests that could be affected by the committee's discussions.

Unlike issues before our committee in which a particular product is discussed, issues of broader applicability, such as the topic of today's meeting, involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact on so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member.

The FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee these potential conflicts are mitigated.

With respect to FDA's invited guests, we would like to disclose that Drs. Bernard Levin, John Baron, and Anil Rustgi, and Dr. David Ransohoff, have reported financial interests in firms which could be affected by the committee's discussions.

Lastly, we would like to note for the record that Dr. George Goldstein is participating in this meeting as an industry representative, acting on behalf of regulated industry, and as such he has not been screened for any conflicts of interest.

With respect to all other participants, including the open public hearing, individuals, we ask in the interest of fairness that they address any current interest or previous involvement with any firm whose product could be affected by the committee's discussions today. Thank you.

CHAIRMAN WOLFE: Thank you, Tom. Now, Dr. Raczkowski will give the opening comments.

DR. RACZKOWSKI: Mr. Chairman, members of the Gastrointestinal Drugs Advisory Committee, and invited speakers and guests, ladies and gentlemen, I am Victor Raczkowski, the Acting Director of the Division of Gastrointestinal and Coagulation Drug Products in the FDA's Center for Drug Evaluation and Research.

And on behalf of the FDA, I welcome you to this meeting of the Gastrointestinal Drugs Advisory Committee. At the Center for Drug Evaluation and Research in FDA, we have an important public health mission.

Our mission in the Center for Drug Evaluation and Research is to make safe and effective drugs available to the American Public. But what does safe and effective mean? What are safe and effective drugs?

In short, a safe and effective drug is one in which the benefits exceed the risks under its labeled conditions for use. So at today's advisory committee, we will keep coming back to several of these themes; the safety of the drug, the effectiveness of the drug, the benefit risks of the drug, and the appropriate conditions for use of the drug.

But the specific purpose of today's meeting is to discuss standards in the design of clinical trials intended to test the efficacy and safety of chemopreventive agents that are being developed to gain FDA approval in reducing the risks of sporadic colorectal cancer.

At FDA, we work with the pharmaceutical industry and with academia in the design, analysis, and interpretation of clinical trials. As such, the FDA is seeking practical advice on how clinical trials should be designed for chemopreventive agents for colorectal cancer.

We at the FDA can then use this practical advice to give guidance to the pharmaceutical industry and to academic investigators on how to proceed with clinical trials. That is a big order, and we have a full day ahead of us.

As a prelude to the Committee's deliberations this afternoon, we have invited several distinguished experts to speak this morning on several topics of interest.

First, Dr. Rustgi will discuss the epidemiology and mechanisms of colorectal cancer. Dr. David Lieberman will then talk about colorectal cancer screening and surveillance.

Next, Dr. Bernard Levin will give us an overview of chemoprevention trials; and finally, Dr. Mark Avigan, of the FDA, will summarize some issues surrounding the benefit risk assessment of chemopreventive agents for colorectal cancer.

We hope to get all four of these presentations in before the mid-morning break. And after the break, we will have time to ask clarifying questions of the presenters, and then to complete the morning, we will hear from members of the public who have requested time to present their views to the committee.

And then after lunch, we will return for the committee's deliberations over the questions that the FDA has prepared for it. We plan to adjourn at 5:30. Now, that is a lot to accomplish in a day, and so we are asking for your assistance in helping to keep us on track in the discussions that we will be having today.

In concluding my comments, I would like to emphasize four points. First, today's discussion is not intended to be a discussion of the general merits of chemoprevention. We would all agree that prevention of cancer would be a public health benefit if it can be done with minimal risks.

Or stated differently, the prevention of cancer would be a good thing overall if the benefits exceed the risks, and if we can describe how the drug should be used.

So instead of a general discussion of chemoprevention, the discussion today is intended to focus on chemoprevention in a particular clinical setting, the prevention of colorectal cancer.

In this clinical setting, the prevention of colorectal cancer, the widespread availability of colonoscopic screening and surveillance poses somewhat unique challenges to the pharmaceutical industry, or

to researchers wishing to develop drugs in this area.

As will be elaborated upon by Dr. Avigan of the FDA, colonoscopy is not a procedure used for screening and diagnosis, but colonoscopy with polypectomy also is used therapeutically to remove colonic lesions before they progress.

As a therapeutic procedure then, colonoscopy with polypectomy complicates designs of clinical trials of drugs because the procedure itself often prevents colorectal cancer.

The procedure itself then achieves the intended goal of drug therapy. And in doing so the procedure significantly complicates the design of clinical trials in this area.

Second, the FDA called today's advisory committee meeting to obtain practical recommendations on how to design clinical studies of chemopreventive agents for colorectal cancer.

As such, we are asking practical study design questions of the committee; what are appropriate end points for clinical trials, what populations should be enrolled in trials; how big of an effect size in clinical trials are clinically meaningful, how should safety be evaluated in clinical trials.

But given the availability of colonoscopy and polypectomy, we seek your comments also on what you think the most appropriate public health use would be of chemopreventive agents being developed for colorectal cancer.

So as you listen to Dr. Avigan's talk this morning, please give some thought as to whether it is in the general interests or the greatest interests of the public health to develop chemopreventive agents as adjunct to colonoscopy and polypectomy, and if so, how can that be done practically.

Or is it in the greatest interests of the public health to develop chemopreventive agents as alternatives to colonoscopy and polypectomy. And if so, how can that be done practically.

Or finally is it in the greatest interests of the public health to develop chemopreventive agents specifically for those individuals who are either unable or unwilling to undergo colonoscopic screening or surveillance.

And again if so how can that be done practically. Third, today's advisory committee meeting is not focused on any particular drug or drug class.

Rather, as I have said, we intend for

today's meeting to be focused on more or less generic clinical trial issues that could be applied to any drug under development in this area.

So if a particular drug or drug class is discussed today, we ask that it be done in a way that illustrates a particular issue or articulates a principle of clinical trial design.

At today's meeting we are not so much interested in debating the merits or lack of merits of any particular drug, or any particular drug class. And finally today's meeting is about chemoprevention of sporadic colorectal cancer.

Today's discussion is not about familial adenomatous polyposis. Thank you, and I look forward to a very interesting and stimulating day.

CHAIRMAN WOLFE: Thank you, Dr. Raczkowski. Our first guest speaker will be Dr. Anil Rustgi, who is a T. Grier Miller Associate Professor of Medicine and Genetics, and Chief of the Division of Gastroenterology, University of Pennsylvania.

He will be speaking on the epidemiology and mechanisms of colorectal cancer. Anil.

DR. RUSTGI: Thanks, Michael, and I would like to thank the FDA for inviting me. I have a tall task to cover the salient features of the epidemiology

of sporadic colorectal cancer, and to touch upon some of the underlying genetic mechanisms.

Many of the pioneers of epidemiology and chemoprevention of colorectal cancer are in the audience, and so my apologies in advance to them if I mis-speak at all.

Apart from providing some introductory remarks about these two areas, I hope then to serve as a transition to the subsequent three talks, and as a platform for this discussion as well.

We often think of colorectal cancer as a primary problem in the United States, but when one reflects upon it, it is indeed a problem throughout the world, and there are approximately 900,000 cases as of at least six years ago throughout the world representing nearly 10 percent of all new cases of cancer.

The incidence rates vary tremendously on a geographic basis, the highest being in North America, Western Europe, and Australia, New Zealand, and Japan. The lowest being in certain parts of South Asia and Northern Africa.

And this plot argues cogently that there are environmental factors, especially dietary in nature, that provide a predilection for this

variation. In terms of mortality, there are approximately 550,000 deaths related to colorectal cancer, and those mortality rates don't vary too much from country to country where colorectal cancer is a problem.

So within the United States, colorectal cancer is the third leading cause of cancer in men, as well as in women. Next slide.

And indeed it is the second overall leading cause of cancer related deaths in the United States, account for 10 to 11 percent of all cancer related mortality.

This figure varies from year to year, but there are approximately 130,000 to 140,000 new cases of colon cancer every year in the United States, with about 56 to 57,000 deaths related to colorectal cancer, either the primary problem, but especially metastic complications to the lung and liver.

Probably as a result of screening and surveillance, both the incidents and mortality rates have been decreasing for colorectal cancer, especially in the last decade. And a point that I will be elaborating upon in subsequent discussions. Next slide.

So if one looks at the average annual age-

specific incidence and mortality rates of colorectal cancer in the early '90s, and this is from the SEER data, one notices a key feature. That with increasing age, incident increases in men and women, and not surprisingly mortality increases, especially above the age of 50.

And there is discordance in the mortality rates based upon ethnic groups. But mortality rates are much higher in African-Americans than those of white Americans. Next slide.

So the key feature in sporadic colorectic cancer is that the predisposing factor is sporadic adenomatous polyps. And indeed one can overlie the graphs for prevalence of sporadic adenomas with that of instance of colorectal cancer.

Such that the prevalence of adenomas above the age of 50 is believed to be on the order of 25 to 50 percent, representing a compendium of a great deal of literature.

And the lifetime risk of cancer at age 50 years, and that is for average risk of women is five percent, and that for average risk of males is six percent. And that the persons with advanced adenomas are at grave risk for colorectal cancer. Next slide.

So what are the risk factors for

colorectal cancer apart from age that I have already mentioned? The other is a personal history of adenomas, as well as a personal history of colorectal cancer. I alluded to dietary factors in the United States and worldwide, and that includes high fat and possibly fiber, although this is come under greater scrutiny in recent years.

Inflammatory bowel disease, where the risk is linked to the extent of disease, as well as the duration of disease, especially in the setting of ulcerative colitis, a family history of colorectal cancer, as well as the hereditary colon cancer syndromes. Next slide.

So that risk of colorectal cancer then varies depending upon the particular factor that one looks at. So if there is a personal history of colorectal neoplasia, it is believed that that risk increases to about 20 percent, and for inflammatory bowel disease, there is a wide range, primarily due to a wide body of studies, and that may be as high as 40 percent.

But in the inherited from of colon cancer, hereditary non-polyposis colorectal cancer, that risk approaches 80 percent. And as you know for FAP, it approaches 95 to a hundred percent. Next slide.

So if we look at the familial risk for colorectal cancer, and here I wish to emphasize that obtaining family history is imperative, and that approximate lifetime risk increases with the nature of the family history.

So that it is around 8 percent for one first degree and two second degree relatives, and if one has two first degree relatives, that risk approaches 17 percent. Next slide.

So it is worth emphasizing the inherited forms of colon cancer because they have provided a lot of insights into the genetic basis of colorectal cancer, and indeed this has served as a paradigm for cancer biology and genetics in general.

So while approximately 75 or 80 percent of all colorectal cancers may be sporadic in nature, or ostensibly sporadic in nature, probably on the order of 20 percent is familial.

And the best known syndrome of an inherited basis is hereditary non-polyposis colon cancer, which accounts for approximately 3 to 5 percent of all colon cancer, that varies from country to country.

FAP represents about one percent, and the rare syndromes, and these are the hamartomatous

polyposis syndromes, predominantly in the pediatric and adolescent population, that account for perhaps less than .1 percent. Next slide.

So FAP an inherited form of colon cancer, in which the hallmark feature is hundreds to thousands of polyps throughout the colon, with an estimated penetrance of greater than 90 percent. This impressionistic depiction that didn't turn out too well is meant to highlight these patients have a sea of polyps.

And unless the colon is removed by surgical needs in his or hers teens or twenties, then nearly a hundred percent of these patients will develop colon cancer, and these patients have an association of extracolonic cancers, predominantly benign in nature, but certainly malignant lesions can be found, especially in the upper-GI tract. Next slide.

So the genetic basis of FAP has been elucidated over the last 15 years or so, starting out with cytogenetic reports, the genetic linkage analysis, to about 11 years ago, where the gene was identified by two different groups as being the APC, or adenomatous polyposis colite tumor suppressor gene, on chromosome 5q.

About a third of the patients have a de novo germ line or inherited mutations, and the remaining two-thirds have some family history. Most families have unique mutations. In other words, there doesn't tend to be a hot spot in the mutations, in contrast to ras mutations in sporadic colon cancer.

And about 95 percent of these mutations lead to a stop code on, and therefore, a truncated protein that has been exploited, in terms of genetic testing. And indeed, depending upon the location of the mutation, there can be some correlation with phenotypic characteristics, especially with ocular findings, as well as desmoid tumors. Next slide.

So this is a schematic of the gene itself. It is a rather large gene compromising 15 exons, and encodes a protein of about 310 kiloDaltons. The gene ubiquitously expressed, but for reasons unclear when mutations do occur in this gene on inherited or germ line basis, the phenotypic features are site specific, especially in the colon.

Arguing for other factors, especially modifier loci, in the germ line that may be affecting the phenotypic manifestations. Nevertheless, in FAP patients, the mutations have a broad spectrum.

But about a third-to-a-half of them are

found in exon 15, and again, these lead to stop codons and truncated protein, so that there is a spectrum in the molecular mass of the protein from anywhere from 80 kiloDaltons to about 240 kiloDaltons.

There is a variant of FAP called attenuated FAP, in which these patients have perhaps 10, 20, or up to a hundred polyps with a later onset and presentation of the polyps, as well as colorectal cancer, that can be associated with upper GI lesions.

And the mutational spectrum is quite fascinating, in that they are found either at the amino terminus or the five prime end, leading to a very short protein that is unstable in nature, or at the extreme, three prime end. And that can also be exploited from a genetic testing viewpoint. Next slide.

So the indications for APC gene testing are those patients in whom you find have FAP or attenuated FAP, and much work has been done by Frank Giardiello, in terms of predictive testing for FAP in the blood relatives of persons with FAP or known APC mutations. Next slide.

So let me turn your attention now to the most common known inherited form of colon cancer, and that is called HNPCC; early onset, but later than FAP.

Typically, these patients are in their mid-forties.

There is a predilection for occurrence of the adenomas, which can number up to a hundred, but typically much fewer in the approximal colon, Perhaps 70 percent are in the approximal colon, and the remaining can be found in the distal colon as well.

And these are the hallmark features of what is called Type-1 HNPCC, and Type-2 HNPCC, shares the features of Type-1, except as accompanied by a number of extra colonic cancers, especially endometrial and ovarian in women.

And in men and women, especially gastric and pancreatic, as well as in the small bowel. When there is the presence of sebaceous skin tumors, that variant is called miratora syndrome. Next slide.

So the definition for HNPCC is one that has been in evolution over the last 11 years, and I won't really belabor that too much, except that about 11 years ago there was some uniform criteria that were adopted, called the Amsterdam criteria.

Suffice it to say thee have been modified to incorporate genetic criteria, the so-called modified Amsterdam criteria. And there are complimentary criteria called the Bethesda criteria.

But as a platform for the definition of

HNPCC for both clinical and genetic studies, these criteria include three or more relatives with verified colorectal cancer.

One case being a first degree relative of the other two, spanning two generations; one case before age 50, and exclusion of FAP. And what we all encounter in our genetics clinics is not so much HNPCC patients, which are fairly straightforward and definitely FAP patients, which are easily defined, but those families that may have some of the features of HNPCC, but don't fulfill the criteria.

And at the current time it behooves us to treat such individuals and families as having HNPCC until more genetic definitions are forthcoming for other forms of inherited colon cancer. Next side.

So the genetic features of HNPCC, like FAP, there is an autosomal dominant inheritance, and the penetrance is about 80 percent, and not as high as FAP. The genes, unfortunately, have led to a complicated analysis of HNPCC.

In contrast, FAP, there is one gene that defines the disease in HNPCC, and there is a compendium of genes, and these are called the DNA mismatch repair genes, of which there are at least six that are known, likely more than exist. And all of

these genes are located on different chromosomes. Next slide.

So if you look further at HNPCC, the vast majority of kindreds that have been studied in Japan, the United States, and especially Finland, are due to mutations in MSH2 or MLH1, accounting for about anywhere from 50 to 70 percent.

But what that tells us is that a third of these families have mutations in genes that have yet to be identified, and do not involve DNA mismatch repair genes that are rarely mutated. Next slide.

So as I alluded to earlier, there are extra colonic cancers that can be found in HNPCC, and that risk increases with age. Obviously, the greatest being for a colorectal cancer, but second being with endometrial and the others that are listed here for you representing a spectrum of sights. Next slide.

And so what is the genetic phenomenon that is observed in HNPCC, which has been elucidated by several groups? And the key underlying disorder is what is called microsatellite instability.

So what happens is that many genes across the genom have mononucleotide, dinucleotide, and trinucleotide repeats, and if errors occur during DNA replication that can be either spontaneous or through

some external insults, such as UV light, or a chemical carcinogen, then DNA mismatch repair enzymes have the ability to repair these mismatches.

But if there are mutations in those genes, they are unable to repair the mismatches, and errors then occur in DNA repair that are transmitted to daughter cells and other progenitor cells.

And that creates a phenomenon, or engenders a phenomenon of microsatellite instability, which in- turn engenders mutations and key targeted genes that have these mononucleotide and dinucleotide repeats, such that nearly a hundred percent of HNPCC tumors, whether colonic or extracolonic, have evidence of microsatellite instability at multiple loci.

And indeed routine MSI assays are available, so that one can test for evidence of microsatellite instability in a tumor of an effected with HNPCC or whom you suspect to have HNPCC.

And then this serves as the basis then for doing genetic testing, especially in MLH1 and MSH2. I should add parenthetically that about 15 percent of sporadic colorectal cancers have microsatellite instability.

So you see a confluence of information from the genetic basis of colorectal cancer to

sporadic colorectal cancer. Next slide.

So in terms of genetic testing for HNPCC susceptibility, most centers will first look for evidence of microsatellite instability, and if that is found, and that is relatively straight-forward, then that serves as an impetus to look for mutations in two of the mis-match repair genes.

And it is only helpful if there is a positive result. If there is a negative result, then you still have to continue close clinical screening and scrutiny because of one-third of patients you won't find a gene mutation. Next slide.

So while understandably the focus over the last 15, and especially 10, years has been on FAP and HNPCC from a genetic basis, and then translating that into genetic testing and predictive markers, as well as chemoprevention, I wish to emphasize that really the vast majority of familial forms of colorectal cancer are not under the perview of FAP and HNPCC.

And it is estimated by many that perhaps 20, if not 25, percent of all colorectal cancers annually form or come under this umbrella. The age of onset may be typical of sporadic colorectal cancer, but it may be earlier.

There will be a huge spectrum of the

extent of family history, and there are multiple causes, and these individuals likely will have few to no adenomas. One thing that we are intensibly investigating is the potential link of familial colorectal cancer in the setting of breast cancer, something that epidemiologically is quite controversial.

Another thing that is being done by Sandy Markowitz and Bert Vogelstein is SID pair studies across the country. And hopefully these sorts of studies will lead to the discovery and identification of different genes that are responsible for other forms of familial colorectal cancer, and will hopefully influence then epidemiology, and especially chemoprevention approaches in the future. Next slide.

So while we have learned a tremendous amount from the inherited basis of colorectal cancer, an equal amount has been gleaned from mouse models of colon cancer.

Certainly there are other animal models of colon cancer, especially in the application of chemical carcinogens to rats. But I am going to just highlight mouse models that have been genetically engineered, such that genes that have been identified as associated with the progression from normal colon

polyp to cancer are targeted or ablated in embryonic stem cells of mice.

So that the phenotypic manifestation that has been observed with several of these model, and indeed there are several, is a recapitulation of either FAP or to a lesser extent, HNPCC.

And the classic one is where the gene that is responsible for FAP has been disrupted, and there are about six such models available. These mice develop not only colonic polyposis, but predominantly small bowel polyposis, as well as demonstrate evidence of extra colonic features.

A molecule that is in the TGF-beta signaling pathway, SMAD has been ablated, and those mice develop polyps and cancer. Interestingly enough when each of the six mismatch repair genes is disrupted in the germ line of mice, there is rarely a recapitulation of the polyposis phenotypic HNPCC, these mice either develop a spectrum of lymphomas or sarcomas.

Or when cross-bred into the APC background, then there is an acceleration of the polyposis. Recently a couple of groups have targeted ras to colonocytes and about 80 percent of the mice developed polyps and cancer.

So much has been learned about the genetic basis of colon cancer through these mouse models, and indeed these have been used intensively to study the feasibility of chemopreventive agents in the preclinical setting. Next slide.

So this paradigm is well known to you and championed by the Vogelstein group about 11 years ago, and modified over time. And that the progression from normal epithelium to different stages of adenoma and eventually to cancer, represents an accumulation of key genetic alternations.

And this is intrinsically bias, because it only takes into account those genetic alterations that are frequently observed, and does not take into account certain biochemical abnormalities that have been studied over the last couple of decades.

But suffice it to say that the key genetic alteration underlying FAP is felt to be perhaps the initiating event in the transition from normal epithelium to a hyperproliferative epithelium.

In fact, studies have shown that perhaps 75 to 80 percent of diminutive polyps harbor APC mutations, and about 40 to 50 percent of small to moderate sized adenomas harbor mutations in the K-ras oncogene, which occur at discreet points in codons 12

and 13.

And that intermediate to late adenomas in cancers have a deletion on chromosome 18q. Initially this was felt to involve the deleted and colon cancer gene.

But now it is clear that it is molecules, the SMAD molecules in the TGF beta signaling pathway that are mutated here, and a later event is p53 mutation, and then when the cancer leaves its primary site to metastasize to lymph nodes and distant organs, other alterations occur, especially in metastasis suppressor genes, and more recently a gene with phosphatase activity was identified.

And this paradigm has been exploited by pathologists, as well as in terms of molecular diagnosis to see if these changes can be detected in the stool of patients at risk for colon cancer.

These alterations, as well as other genetic alterations are being pursued to see if they can be detected in the peripheral blood of patients at risk for colon cancer. That remains a tall order at the current state. Next slide.

So the sporadic adenomas polyp does take time to develop, perhaps up to 10 years, and perhaps less. Not all polyps develop into cancer as you know,

perhaps 8 to 10 percent do, and that the risk factors for the polyp to cancer progression are predicated upon the size of the polyp, as well as the histology of the polyp. Next slide.

So we often talk about surrogate markets for chemoprevention, and focus upon polyp, in terms of our ability to effect the size of the polyp, as well as the number of polyps.

And what I would emphasize is that the transition for understanding the feasibility of chemopreventive agent occurs naturally from preclinical settings, especially in the genetically engineered mouse models, to the inherited forms of colon cancer.

And then eventually as is the focus for today's discussion, to the sporadic or general population. While understandably it is important to look at the size and number of polyps, I would like to emphasize that there are other biomarkers to investigate in the normal colonic mucosa, as well as the polyp.

And these can be looked at at the DNA, RNA, and protein level by a number of different techniques related to proliferation, differentiation, apoptosis, and this has served as the basis for

intensive investigation by both companies and investigators to apply microarrays or functional genomics.

Finally, looking at biomarkers in the stool and blood remains currently investigational. Next slide. So I will conclude to highlight the risk factors for colon cancer.

Think of it as a partition between inherited forms and acquired, especially sporadic adenomas polyp. The genetic basis for colon cancer includes obviously FAP and HNPCC, but yet to be defined forms.

The transition from normal polyp to sporadic polyp, to colon cancer, involves different pathways, and that one needs to emphasize pre-clinical models for colon cancer, in terms of testing feasibility. Next slide.

And that the applications of chemoprevention initially occur in animal models, to the inherited forms of colon cancer, and that the determination of the efficacy of chemoprevention involves a whole panel of surrogate markers. So I will conclude there and thank you for your attention.

(Applause.)

CHAIRMAN WOLFE: Thank you, Dr. Rustgi.

We will have time for questions for all the speakers after the break. Our next speaker will be Dr. David Liberman, who is a Professor of Medicine, and Chief of the Division of Gastroenterology at the Oregon Health Sciences University.

He is also President of the American Society for Gastrointestinal Endoscopy, and he will be speaking on colorectal cancer screening and surveillance. David.

DR. LIEBERMAN: Good morning, and thank you for the invitation to participate in this meeting. I am going to address the subject of screening and surveillance in the average risk population. If I could have the first slide.

And I want to begin by highlighting I think what we have learned over the last decade, and that is that this progression as Dr. Rustgi eloquently described from normal colon, to advanced adenoma, to cancer, which may be mediated by many events, can be interrupted. Next slide.

Now, we can interrupt this if we can identify patients that have advanced adenomas and remove these adenomas. We now have evidence that we could actually prevent cancer with colonoscopic polypectomy. Next slide.

So as we think about these screening tests, I believe that we have to look at a higher bar than we have traditionally looked at. When screening was first introduced in the late 1970s, the goal was early cancer detection, hoping to detect lesions at an early incurable stage.

I think we now have to look at screening and all the screening tests that we have available to us from the perspective of prevention. Next slide. And with that in mind, we have a large list of screening recommendations that have come from a variety of different bodies, advisory and expert bodies, that have reviewed them.

The two most commonly used tests are the fecal occult blood test, and sigmoidoscopy, but other tests have also been recommended, and the most current recommendations include a menu, if you will, of all of these options.

So I would like to review these options briefly with you. Next slide. First, the fecal occult blood test. We have for this test several randomized control trials which have all demonstrated the same thing, and that is that cancers that are detected in screening populations are detected at an early stage compared to unscreened populations.

And that that has translated into a mortality reduction which in the studies has ranged from 15 to 33 percent. There are some differences between these trials, but they all show the same trend.

The test is relatively easy to perform, and it can be completed by primary care providers, making it very attractive. Next slide.

The problems with this test are that it has relatively poor sensitivity for one time testing, and I will show you some data from the cooperative study later, but basically what we found in that study was that the detection of advanced neoplasia with one-time testing was only 24 percent.

And that is an important limitation, which means that for this program to be effective, it has to be repeated on a regular basis, probably annually to be effective based on the studies that are available, and that is a big problem, because compliance with repeat testing and clinical studies, and in real life clinical practice is quite poor.

In addition, although this test on the surface appears to be very inexpensive. There are many hidden costs built into the evaluation of these tests, and repeating the tests and developing programs

for setting up repeat testing that create increased costs. Next slide.

Sigmoidoscopy, which is the other most commonly used screening test, the evidence in favor of it comes from case control studies, and not randomized control trials. But they are well done and demonstrated at a 60 percent reduction in colorectal cancer mortality in that portion of the colon that was examined with the sigmoidoscope. Next slide.

The advantages for this are that we can not only detect early cancers, but we can also detect advanced adenomas, which could be removed in leading the cancer prevention.

It can be performed by primary care providers and non-physicians. The limitations are that it only examines one-third of the colon, and therefore approximal lesions may not be detected. Next slide.

In the VA cooperative study that we completed over the last few years, we performed screening colonoscopy in a large cohort, over 3,000 asystematic men, between the ages of 50 to 75, with a goal of determining how many patients with advanced neoplasia would be detected with either a fecal occult blood testing or a sigmoidoscopy.

And what we found was that sigmoidoscopy, if you use sigmoidoscopy alone, and we assumed that if any adenoma was found in the lower part of the colon that would lead to a full colonoscopy, the detection rate was 70 percent of patients with advanced adenomas.

For fecal occult blood testing we found as I mentioned earlier that the detection rate was only 24 percent, and of course this highlights an important limitation of one-time testing, which is not what has been recommended.

And finally for combined testing, we found that if you had combined the fecal occult blood testing and sigmoidoscopy there would have been a detection rate of 76 percent, meaning that about a quarter of the patients with advanced neoplasia would not be detected with one-time testing. Next slide.

The other recommended tests include a barium enema, and for this I can't present any data because there is none in the screening population. We do have some evidence from the national polyp study thought that tells us what about 50 percent of patients that have adenomas greater than one centimeter are not detected with barium studies.

And I think this is an important

limitation since we know that this population of patients does have a higher risk of either having a malignancy in the polyp or developing malignancy. Next slide.

Now, we have some other potential ways of imaging the colon which are not in the standard recommendations, but which are currently under study. Virtual imaging of the colon with CT scanning as shown in this slide, and this is an endoscopic picture of a polyp, and unfortunately this does not project well.

But this is a virtual image of the polyp using CT colography, and on the next slide, is an image of another polyp using MR technology. So clearly these imaging modalities have the ability to visualize polypoid growths in the colon. Next slide.

And perhaps their most attractive feature is their name. The concept of virtual really appeals to the public, as opposed to real. And so if that gets people into getting screened, that is not a bad thing necessarily.

The tests so far, and these modalities are still under study, seem to suggest that the sensitivity for large polyps is reasonably good, somewhere between 65 and 95 percent, depending on the

study. It can be performed very rapidly.

The problems with this I think that require further evaluation are summarized in the limitations here. The cost effectiveness is very uncertain, and the analyses that have been done so far suggest that it is not likely to be cost effective, because this modality is so expensive, and patients who are found to have polypoid growths are going to need to go on and have colonoscopy examinations.

The false/positive rate obviously increases the cost, and this includes the detection of small polyps that may not be neoplastic, like hyperplastic polyps, which can be detected with these tests, and that leads to what I described here as the small polyp dilemma, that the radiologist suggests that these can be ignored, although I think most clinicians will have a difficult time ignoring them.

There is some minor patient discomfort with this, and right now this requires -- the CT colography requires a full prep of the colon. That may be changed over time, but right now I think this modality still requires further study before it should be implemented. Next slide.

Finally, the idea of screening with colonoscopy has emerged over the last few years, and

we have known for a long time that this is probably the most effective test for identifying polypoid growths in the colon, and then actually removing them.

And we have some indirect evidence for effectiveness of colonoscopy, and its obvious limitations relate to risk cost and resources. Next slide.

The data that exists right now for screening colonoscopy comes from several sources, but these are the two largest trials that have been published to date in which large asystematic populations have been screened.

This is over 5,000 patients with colonoscopy, and in experienced hands these data suggest that the majority, or by far the majority of these exams can be complete, and the detection rate for advanced neoplasia in these two studies was quite high, suggesting that there would be a reasonably high yield of identifying patients with lesions that might be considered clinically important. Next slide.

The evidence for effectiveness as I mentioned is indirect, and it comes from I think three major sources. Next slide.

From the National Polyp study, we have evidence that in patients who underwent a complete

colonoscopy with polypectomy, that the expected incidence rates of cancer were sharply reduced over the next six years, from between 76 and 90 percent. Next.

From a study performed by Joe Selby in Oakland, using sigmoidoscopy, they concluded that sigmoidoscopy, which is an endoscopic exam of the distal colon, reduced mortality in that portion of the colon that was examined.

If we extrapolate those results, and we say, well, what if more colon was examined, could you further reduce mortality, I think that is a reasonable, plausible, assumption that perhaps would provide a little bit more evidence that a more complete exam of the colon would be more effective.

And finally in the next slide we have studies from the fecal occult blood test trials which suggest that screened patients had a reduced mortality, which was demonstrated early on, but later were also found to have reduced incidents.

And the authors attributed this to the detection and removal of polyps with colonoscopy. Remember that all the patients in these trials had colonoscopy as their primary evaluation for a positive screening test.

So colonoscopy was probably what reduced mortality in these studies. So again these are direct randomized control trials or case control studies, but they provide some evidence that colonoscopy could be very effective. Next slide.

So in summary what we found in the VA cooperative study, and I think what has been known epidemiologically, is that the prevalence of advanced neoplasia increases with age.

That the prevalence of approximal advanced neoplasia increases with age. The more patients with advanced neoplasia go undetected with fecal occult blood testing and sigmoidoscopy as they age, and this was a finding that was not unexpected from the VA study, but it suggested that these tests are not going to be quite as effective as we get older because of this increased approximal advanced neoplasia.

And finally that colonoscopy might be a more effective screening test, which is what the VA study demonstrated, after the age of 60. Next slide. Now, whatever method that we choose to use for screening, whether it is FOBT, sigmoidoscopy, colon imaging, fecal markers, or a colonoscopy, it is going to lead to a colonoscopy.

So we are going to have a lot of

colonoscopy, and that is going to result in the detection of polyps which is going to lead to surveillance colonoscopy afterwards. Next.

So I think that I want to conclude by talking about several issues that I think come out of the screening studies, and that is the question of what to do about surveillance, and what about risk cost and resources if we are going to be doing all this colonoscopy. Next.

Regarding surveillance, we have the following recommendations that really are based more on expert consensus than they are on evidence. And that is that most patients who have had adenomas detected should have follow-up colonoscopy at about 3 years, although for patients with only small adenomas perhaps a longer interval is quite safe.

As I said these data really come from expert consensus. What is interesting is that surveillance, when you look at the programmatic costs of all the programs that I just outlined, surveillance is actually pretty costly.

It represents about 20 to 50 percent of the cost of the colon screening program. And if you look at what the patients that are subsequently undergoing surveillance, if we took the VA cooperative

study data, and we asked that among the patients with neoplasia, and these are all the patients that had neoplasia in that study, we had 10.6 percent that had advanced lesions.

But that meant that 72 percent had only small adenomas less than one centimeter as their primary lesion. And we do have some evidence that this group of patients may not be at particularly increased risk for subsequent cancer greater than the population at large, and do these patients all need to have surveillance.

And so I think we need further study on this. But obviously if we had some form of intervention that would reduce the rate of these patients appearing for surveillance, that that could have an impact on cost. And theoretically that is one way that chemoprevention might play a role. Next slide. So I think we have pretty good evidence that surveillance has an important impact on the cost of screening programs.

That it is going to have a huge impact on available resources for screening. If we do more screening, we are going to end up doing more surveillance.

And that is going to stretch the resources

that we have available to perform screening examinations. There is evidence that the risk may be low for patients with small adenomas, and we need more evidence to make us confident that we don't need to do surveillance in this group. And perhaps it could be modified or reduced with chemoprevention. next slide

The risk of colonoscopy has come from a variety of sources, mostly from surveys. I will present you the data from the VA cooperative study that we just published this month in Gastrointestinal Endoscopy.

In almost thirty-two hundred examinations in patients who with a mean age of 63, and on to the next slide, and we found the following major complications. the overall definite complication rate, or in other words, complications that were clearly related to the colonoscopy, was 0.3 percent.

And almost all of those were related to performance of polypectomy. The vast majority were bleeding after a polypectomy, that resulted in either hospitalization, transfusion, or surgery.

There were some important cardiopulmonary complications associated with it. So this is not a trivial procedure, and there is risk associated with it. If we just look at the diagnostic studies. In

other words, where no polypectomy was performed, the overall complication right here was only 0.1 percent.

And if we add up all these complications, and those that were definitely related, and those that might have been, the overall complication rate is 0.5 percent.

So we have a significant complication rate most often associated with polypectomy. Next slide, please.

If we compare that to prior studies, it is actually a little bit lower than has been reported previously. This is a compilation of significant bleeding from prior studies, and the VA studies at the low end of this, and for perforations, this is the rate that has been reported.

We didn't have any, but obviously perforation can occur as a risk. The means of controlling risk right now are improving training and performing quality improvement. But obviously if we didn't have to do as much polypectomy, which is the primary source of this risk, we could modify this risk and potentially have fewer complications. Next slide.

The other question that is often raised about screening is can we afford it. Next slide. And I would twist this question around and ask can we

afford not to screen.

We know that when cancer occurs in patients that there is a cost of cancer care, and the current estimates in the United States range somewhere between 50 and 80 thousand dollars for each case of cancer that is detected.

But in addition there is emotional costs, and of course there is this missed opportunity that we have for prevention. The next slide. If we compare the cost of cancer screening to other things that we do in medicine, such as colon screening, whichever way you do it, seems to compare very favorably. So this is looking at the cost per added year of life, which is a common way of looking at cost effectiveness, and comparing colon screening with other things that we do, including hypertension management, mammography, and cholesterol management.

And as you can see, colon screening seems to compare favorably to other things that we do in medicine that we consider standard of care. So I would twist the argument around and say that we can probably afford that we need to consider screening, and that costs are really cost effective.

And in fact, if we can actually prevent a lot of cancers, either with screening or

chemoprevention, that it may even be cost saving. Next slide.

The last point that I want to make is related to the resources for screening. If we actually did achieve high rates of screening in the United States, and by the way the current screening rates in the United States are somewhere between 40 and 50 percent, compared to mammography and cervical cancer screening rates of 60 to 75 percent, we might have a problem. And this has been cited by a number of experts that the new demand for colonoscopy as a result of screening might completely overwhelm the capacity that we have. Next slide.

One way of looking at this, and this is only one perspective, is if we take a look at what we are doing colonoscopy for now. This is some data that we generated from an NIH funded National endoscopic database.

Now, this is a data repository in which 80 practice sites around the United States send endoscopic data to Portland, Oregon. It goes into a repository and we are able to take snapshots of what happens when procedures are performed, and why they are performed.

So this represents data from two years,

from 2000 and 2001, and about 50,000 colonoscopy examinations that were performed during that time. And this is a breakdown of the indications.

If we look just at the screening indications in yellow, you can see that they account for right now a relatively small percentage of the procedures as they are indicated here.

If you look at some of the other indications though and you ask could we actually shift some of these resources into screening, some of the patients that are currently getting evaluations for bright red blood, pain, diarrhea, or even polyp surveillance, if they were undergoing screening examinations, you might not need to have these examinations.

So I think there is potential when you look at this overall current utilization of colonoscopy for shifting resources, and making more colonoscopy resources available for screening. Next slide.

And one example of that is related to surveillance. I showed you data from the VA study before suggesting that 72 percent of asymptomatic men in our study had only small tubular adenomas, with a low associated risk of cancer.

If we could shift some of these resources from surveillance to screening, we may get much more bang for our buck. Next slide.

And potentially we could even out this little slide here. So that the demand and the capacity issues, the capacity could be increased by shifting resources, and perhaps improving efficiency in the way that we deliver our colonoscopic resources. So the next slide.

So to summarize the screening guidelines, we have among the screening modalities that have been offered, randomized control studies for fecal occult blood testing, a potential mortality reduction in the 20 to 50 percent range, but some problems.

That it is not a very good cancer prevention test, and that it needs to be repeated. For sigmoidoscopy evidence is case control, and we have the potential mortality reduction of 50 to 55 percent, but we are going to miss patients with proximally neoplasia.

Imaging studies. We have really no evidence right now. We can only guess at potential mortality reduction, and there is going to be cost issues. For colonoscopy, the evidence is indirect.

We have the potential here though for much

cancer prevention, and therefore much more mortality reduction, but it is invasive and higher risk. Next slide.

Now, as we look at this paradigm and think about how chemoprevention might affect screening, and going to the next slide, one of the most obvious ways that we would like to see it affected would be to impact these two areas here, the progression.

And we know that adenomas are very common, but if we could interrupt the progression to advance the adenoma, or to advance the adenoma to cancer, that would be extremely attractive.

And obviously if there is a direct pathway from normal to cancer, we would like to interrupt that. This pathway here, this normal to adenoma, is potentially interruptable with chemoprevention.

The question would be is that important, and that is going to be an important subject for discussion here today. I would argue that it could be because the vast majority of patients that we find with adenomas end up having small tubular adenomas as I demonstrated.

If we could reduce the burden of this, it would reduce the burden of polypectomies that need to be performed, and therefore the risk. It would also

reduce potentially the need for surveillance in this population of patients.

And then finally, chemoprevention could obviously have an impact here on surveillance of patients that are found to have adenomas, and perhaps reduce the burden and the need for surveillance. Next slide.

So to summarize, I think we have evidence currently that screening can be very effective in reducing mortality and potentially preventing cancers. However in 1999, only 44 percent of adults, age 50 and older, had at least one of the recommended tests at the appropriate interval.

So we have a big problem with compliance that I think creates obstacles to achieving effectiveness of screening programs. For many of these patients screening may never been something that they choose to have, and perhaps other methods of preventing cancer need to be considered, and at least in a complimentary way with screening or perhaps instead of screening for those that don't want it. Next slide.

And finally I think the challenges regarding screening for the future are summarized on this slide, and obviously it would be ideal not to

screen everybody, but to only screen those patients most likely to develop cancer.

Dr. Rustgi presented some elegant data about how we might do that in the future but certainly risk stratification would be important. If we could identify risk factors, we could also develop risk reduction strategies.

Developing new tools for screening. You have genetic markers, and circulating proteins, or new imaging, may be important. But the bottom line for screening is going to be whatever tests we end up using, we are going to have to get the public to buy into it. Thank you very much.

(Applause.)

CHAIRMAN WOLFE: Thank you, David, most importantly for an outstanding lecture, and secondly, for getting us back on schedule. Our next speaker will be Dr. Bernard Levin, who is the Vice President for Chemoprevention, and Professor of Medicine at the University of Texas, M.D. Anderson Cancer Center.

And Dr. Levin will speak on the overview of chemoprevention trials. Bernie.

DR. LEVIN: Mr. Chairman, members of the G.I. Advisory Panel, invited guests, ladies and gentlemen, I would like to compliment the FDA on

engaging us in this dialogue, because I think this is a very important topic which requires a considerable amount of attention and will undoubtedly lead to a quite intense debate.

Over the past decade or two, we have learned much about carcinogenesis as a chronic disorder, and more specifically in the colon, about the implications of the dysplasia-Carcinoma sequence.

Eloquent molecular studies and endoscopic studies have contributed to this. In the discussion today about chemoprevention, it will reflect the work that has been done in a collaborative way between investigators at academic institutions, the National Cancer Institute, industry, and in many ways represents a synthesis of a great deal of this information.

And I think it is a very exciting time to be looking at the issue of chemoprevention. Whereas, a lot of efforts have been focused on the treatment of established cancer, I think we are now beginning to understand the importance of trying to evaluate the possibilities of intervention at the earliest possible stages. Next slide, please.

With advancing knowledge, we have begun to define targets for chemoprevention, and they include

genetic mutations, about which you have heard, potential growth factors, and other resectors, and key enzymes, including the cyclooxygenase enzymes 1 and 2. Next slide, please.

With specific attention to the anterior plastic effect of aspirin like drugs, a number of Cox-dependent and independent mechanisms have been developed. Cyclooxygenase 1 and 2, and its role in prostaglandins metabolism has now been well defined.

There are also important known cyclooxygenase targets, including the PPARs, and these are all interacting to influence apoptosis, proliferation, angiogenesis, and carcinogen activation, and eventually the process and development of neoplasia and cancer.

We have learned a lot about the possibilities of how to intervene in these various pathways, both at the in vitro level, in animal models, and now beginning in human trials. Next slide, please.

There is a considerable amount of evidence suggesting epidemiologically that long term use of non-steroidal anti-inflammatory drugs, Cox inhibitors, reduce colorectal neoplasia.

And in a most recent study from Spain, a

79 percent reduction in the relative risk. Next slide, please.

This observational data is also extended to cancer incidents, both in prospective and retrospective trials. Next slide, please. And also in mortality, cancer-associated mortality. This body of data is extremely consistent, and crosses different countries, and across genders, and across different time points. Next slide, please.

We also know that the Cox-2 inhibitor has been shown experimentally to inhibit tumor multiplicity in one of the models that has been mentioned earlier by Dr. Rustgi, and comparing a Cox-2 inhibitor with the more traditional non-steroidal anti-inflammatory drug.

This effect is seen both in the early treatment, as well as in the late treatment of animals who have this genetic lesion. Next slide, please.

Cyclooxygenase-2 as a molecular target has been found to be over-expressed in human neoplasia, both in pre-invasive neoplasia, and invasive neoplasia, in the upper digestive tract, gastrointestinal tract, the colon and rectum, consistent studies both in early and late neoplasia. As well as other organ sites. Next slide, please.

In a study that was done in collaboration with the National Cancer Institute, St. Marks Hospital, Pharmacia, Searle, and M.D. Anderson Cancer Center,

Cyclooxygenase-2 was shown at a dose of 400 milligrams twice a day to reflect a change in both number and size of adenomas, in a group of patients treated for six months who had familial adenomatous polyposis.

This subsequently led to approval by the Food and Drug Administration of celeboxib as a pharmacological adjunct in the management of patients with familial adenomatous polyposis. Next slide, please.

As you heard there are a number of potential end-points for understanding and evaluating the mechanisms of treatment with chemopreventive agents, and they include adenoma number, adenoma size, and other markers, including cellular markers, and molecular markers, and now with genome array or proteomics array, and other biochemical markers.

I am going to focus now on adenomas. Next slide, please. And already mentioned by Dr. Lieberman, in the results of the national polyps study intervention, where it was shown that there was a substantial reduction in the number of observed

cancers in this group of patients followed for approximately seven years in this report.

And compared with those expected from SEER, St. Mark's, and Mayo Clinic data. These are not concurrent controls, however. Next slide, please.

Now, to turn to the current sporadic intervention trials, sporadic adenoma intervention trials, these have several characteristics. They are international, multicenter, and placebo controlled, and they are aimed at the secondary prevention of sporadic colorectal adenomas.

I am going to summarize three of these. The rofecoxib study began in 2000, April, and includes approximately 2000 patients from 110 centers, and is comparing placebo with rofecoxib 25 milligrams a day.

Colonoscopic evaluation is performed at one year and three years, and the primary end point is the number of adenomas observed at each time point. Next slide please.

The National Cancer Institute study of sporadic adenomas is being conducted in conjunction with Pharmacia, begin in late 1999, and has enrolled almost 2000 patients from a hundred centers, comparing placebo with 200 milligrams twice a day, and 400 milligrams twice a day of celecoxib.

Colonoscopy is performed after 1 and 3 years, and the primary end point is again the number of adenomas. Next slide, please.

An industry supported study by Pharmacia began in March 2001, and fifteen hundred patients have been enrolled and randomized. The placebo is compared to 400 milligrams daily, and colonoscopy is performed at 1 year and 3 years, with a primary end point being the number of adenomas. Next slide, please.

A little more detail on this study. The primary objective in more detail is to evaluate whether celecoxib is safe and effective in reducing the occurrence of new adenomas in subjects who have previously undergone a polypectomy.

And with secondary objectives the number of adenomas, and the histopathologic grade, and the size of the colorectal adenomas at 1 and 3 years. Next slide, please.

Inclusion criteria include age 30 and older, attention being given to the endoscopic quality of the examination, with photography of the cecum; measurement by forceps or slide ruler of the lesion, has to be over six millimeters as a single lesion, or more than one polyp of any size based on risk modeling data.

People included have to abstain from long term NSAIDs or COX-2, with the exception of low dose aspirin. Next slide, please.

There is stratification for low dose aspirin use into celecoxib, placebos, or no aspirin use, and again in to celeboxib or placebos. Next slide, please.

As an example of how these studies are constructed, here is the study time line overview with the time provided for the initial enrollment of the colonoscopy and polypectomy approximately 120 days, with a placebo lead-in period, then randomization, and then surveillance at 1 year and 3 years after randomization. Next slide, please.

Under development are a number of other chemopreventive agents which may be of interest to you. They include COX inhibitors and other agents, and these studies are being carried out at a number of institutions, both at the National Cancer Institute, and by industry, and at university centers in this country and abroad.

And they include nimesulide, deoxycolic acid, meloxicam, and nabumetone, and other agents include some of the statins, matrix of metalloproteinase inhibitors, growth factor receptor

kinase inhibitors, and others.

These are in the preclinical phases. In phase one and two, they include combinations of non-steroidals, and difluromethylornithine, as well as other agents.

And then further Phase 3 studies have already alluded to a couple of these, but they include studies of aspirin, as well as ursodiol, sulindac sulfone, and selenium, and very few studies have made it to Phase 4, and perhaps calcium is just one example. Next slide, please.

The potential role of interactions of these combinations is now under study, and this is one example of the use of COX inhibitors and difluromethylornithine in animal models of colorectal cancer prevention.

And these are being studied now for the first time in human studies of colon, as well as esophageal premalignancy. Next slide, please.

To give some examples of current NCI sponsored prevention trials with COX-2 inhibitors being conducted at a variety of centers, including those that have been completed.

That one, including those that are under study on familial polyposis, hereditary non-polyposis

colon cancer, sporadic adenomas, and this is the study that I alluded to, the NCI study led by Dr. Monica Bertagnolli, and another sporadic trial led by David Alberts, combining selenium with celecoxib. Next slide, please.

These are some of the trials looking at extracolonic sites, including esophageal, Barrett's dysplasia, and another esophageal study, prostate cancer, superficial bladder cancer, actinic keratosis, and basis cell neva syndrome.

These agents mostly COX-2 inhibitors with a primary goal of looking at dysplasia as a marker, and regression of such lesions. And they are mostly in Phase 2, and some in Phase 1 as well. Next slide, please.

And there are additional trials on patients who have undergone resection of lung cancer, and those with lung dysplasia, and breast cancer is looking now at a marker of rectal neoplasia, aberrant crypt foci, as well as some other miscellaneous lesions.

So there is a variety of trials underway both in the colon and extra colonic sites. Next slide, please.

I would like to address for a moment the

possible roles of a chemopreventive agent in the management of colorectal neoplasia. Clearly improvement of quality of life is most important, and to do this, we want you to reduce neoplasia incidents in mortality.

These agents may have effectiveness in delaying or complimenting initial screening, by complimenting endoscopic surveillance as we have heard from Dr. Lieberman, and by improving effectiveness.

And even in the best of hands there is a 10 to 15 percent mis-rate of adenomas, usually small ones, and more particularly flat adenomas. It would be ideal to reduce procedure related morbidities and inconveniences, in terms of the time of the procedure, the sedation required, and thus the complications.

And possibly in the future to prolong and to examine intervals. In very highest patients, particularly those with inherited defects, spare or delay primary prophylactic polypectomy, or second recolorectal surgeries, such as those associated with the duodenum, by inhibiting or retarding extracolonic neoplasia. Next slide, please.

There are tensions to be considered in the evaluation. Scientific rigor demands that we be accurate, and reproducible, and we can quantify the

benefits, and that we can with considerable accuracy, provide predictive insurance.

On the other hand, in the discussion of trials of chemoprevention, there are issues of scientific practicality, and the time taken, and the number of people who are willing to enroll in such studies, the financial underpinning of such studies, and a moving landscape of early detection, screening, and other factors. Next slide, please.

Intermediate end-points need to be considered broadly and an example from cardiovascular disease, which is described in the FDA and the Endocrinologic and Metabolic Drugs Advisory Committee, is an interesting one and may have application in the considerations that we have today.

This committee previously recommended, and the Food and Drug Administration concurred, that approval of lipid-altering agents should be based on a drug's biochemical efficacy and decreasing serum lipids.

Attempts to establish clinical efficacy and the prevention of coronary artery disease or other manifestation of atherosclerosis, would require prolonged observations, and hamper research and development of this class of drugs. Next slide,

please.

As we consider the development of chemopreventive drugs in populations at risk. We can look at the general population, and where we have heard there is an approximate 40 percent incidence of adenomas, and where we might want to think about a primary prevention.

And there might include dietary and other lifestyle factors, including possibly calcium folate and physical activities, and other factors. We want to focus here on the least harmful, if at all, and what to be assured that this applies to the greatest population.

Moderate risk individuals might be those with current or prior adenomas, people who have had a previous cancer, and where the lifetime risk is greater than the standard risk, which is approximately 5 percent, and here it is about double or triple.

And secondly prevention may be most important, including some of the kinds of agents that I have already described.

And then finally the high risk groups, with inherited disorders, require their own special attention, and again both surgical and pharmacological management have their roles. The last slide, please.

I would like to refer you to a recent American Association of Cancer Research Task Force document, which is actually included in some of the material that you received, where very thoughtful conclusions were reached about the value of risk reduction trials.

And to quote from this, "In colorectal cancer risk reduction trials, the adenoma is a disease end-point, a point of clinical intervention and risk, and perhaps an ideal goal might be in initial studies to show a 30 percent relative reduction in adenoma incidents."

"But other potential clinical benefits might include a decrease in the number of polypectomies and procedure related risks, a delay in time to adenomas, which malignant potential, particularly advanced adenomas, an increase in intervals between surveillance procedures, as well as organ preservation." Thank you for your attention.

(Applause.)

CHAIRMAN WOLFE: Thank you, Dr. Levin. Our next speaker will be Dr. Mark Avigan, who is a Medical Officer in the Division of Gastrointestinal and Coagulation Drug Products, Center for Drug Evaluation and Research.

Dr. Avigan will speak on benefit and risk analysis for chemoprevention of sporadic colorectal cancer.

DR. AVIGAN: Thank you. My name is Mark Avigan, and before I came to the FDA, I served on the faculty at Georgetown as a Board Certified gastroenterologist. Now, approval of drugs by the FDA for the chemoprevention of colorectal cancer depends on adequate controlled clinical trials, which demonstrate a favorable benefit risk assessment in defined populations of patients.

Today, in order to develop a conceptual approach to the development of a benefit risk analysis of chemopreventive agents for the prevention of colorectal cancer, which I will refer to in my subsequent slides as CRC, I intend to touch on the following areas.

First, there are important public health concerns surrounding the addition of chemopreventive agents to the mix of other cancer prevention strategies which we heard about today, including colonoscopic screening and surveillance.

Second, there are important issues that must be taken into account, which are fundamental to a useful efficacy and safety analysis of chemopreventive

agents. These include a discussion about the value of adenomas as efficacy endpoints, and the parameters of an adequate safety analysis.

I shall highlight criteria for FDA approval of two agents for the prevention of specific neoplasms before listing unresolved issues concerning the chemoprevention of sporadic colorectal cancer that need to be addressed today by the committee.

As a public health matter, it is essential that chemopreventive treatment does not displace colonoscopic screening and surveillance if the suppression of cancer by the agent is not as effective as the screening program.

Patients treated with a chemopreventive agent who mistakenly decides to avoid colonoscopic examinations of an impression that they are not necessary may be subjected to a worsening of their cancer risk.

Finally, because only a small proportion of treated patients would be destined to develop colorectal cancer, the risk attached to treat it with a chemopreventive agent of many outweigh the theoretical benefit to a few.

What are potential clinically meaningful benefits from drug administration? There are three

basic categories of possible benefits, depending on whether patients undergo colonoscopic screening and surveillance.

The first is adjunctive cancer prevention, in which the drug should provide an additive effect in the reduction of risk for colorectal cancer, or colorectal cancer mortality to the standard colonoscopic screening and surveillance.

In some cases it might be justified to relax screening and surveillance guidelines, enabling an older age of initial screening, and/or increased time intervals between examinations without a worsening of cancer risk.

The second is alternative cancer prevention, in which the chemopreventive agent is substituted for colonoscopic screening and surveillance. For those who would otherwise be colonoscoped, elimination of screening and surveillance must not compromise cancer risk.

In some cases, alternative treatment might be justified because of an advantage in the drug safety profile, compared to colonoscopy, without compromise of cancer risk, and something which Dr. Lieberman alluded to before.

Finally, there are patients who are unable

or unwilling to comply with colonoscopic guidelines, and in this group the benefit of cancer risk reduction must outweigh the risk of developing serious drug adverse events. Next slide.

Clinical study designs for the evaluation of chemopreventive agents must be compatible with the intended treatment indications. In planning a suitable analysis of efficacy in clinical trials, the following elements must be taken into consideration.

First, the study population. This can either be comprised of individuals who are at normal or increased risk for the development of sporadic colorectal cancer.

Second, the planned end-points of the study should be considered. These can be clinically significant end-points, such as cancer, or surrogates, such as small adenomas.

Third, background management and treatment must be considered. For example, colonoscopy has a profound impact, both on the monitoring of end points and the potential benefit of the test agent.

In addition, medications with possible chemopreventive properties such as low-dose aspirin, may influence the benefit of the study drug. Finally, a sufficient duration of treatment must be planned

that will allow detection of a meaningful change, either pre-malignant or malignant lesions.

Results of short term studies cannot determine whether adenoma suppression and responders is durable. This can only be illuminated by studies of sufficient duration.

If surrogate measurements are used as primary end points, they must reliably predict cancer risks or be validated by measurements of cancer or cancer mortality.

The following elements must be taken into account if incidents of colorectal adenoma reoccurrence after baseline colonoscopic removal of polyps is used as a surrogate for a cancer risk. First, the probability that a small adenoma, less than half a sonometer in diameter, contains high grade dysplasia, or malignant changes in individuals not treated with a chemopreventive agent in the U.S. is less than one percent.

Second, the average transition time from small adenoma to invasive cancer has been estimated to be greater than 10 years. Finally, in the national polyp study, despite reduction of recurrent cancer risk after a cleaning colonoscopy, and that is the baseline colonoscopy, the percentage of patients with

recurrent small or medium adenomas without advanced pathological features was over 30 percent.

Therefore, although colonoscopic screening and surveillance effectively prevents most malignant lesions, the recurrence of adenomas is common. Next slide.

The study size that is needed to measure efficacy of a drug depends on the incidence of neoplasms in the treated population. In familial adenomatous polyposis, in the absence of prophylactic proctocolonectomy as we heard from Dr. Rustgi, the cumulative lifetime risk of adenomas approaches a hundred percent.

It is not very different than the risk to develop cancer. In contrast though, the prevalence of sporadic adenomas approaches 50 or 60 percent in the background geriatric population.

The cumulative lifetime incidence of colorectal cancer is only 6 percent. Because of their high incidence in polyposis patients, the number of patient years needed to detect, say, a 50 percent reduction of either adenomas or cancer, is estimated to be in the range of 2,000.

Likewise, the number of required patient years to measure a 50 percent reduction of sporadic

adenomas is approximately 3,000. In contrast, because of the relatively lower incidence of sporadic cancer in the background population, the number of patient years needed to measure the same degree of cancer suppression is in excess of 30,000.

This requirement for a large study holds true even in the absence of any prevention or screening strategies. Next slide.

As Dr. Lieberman described earlier in his presentation, an important advance in the quest towards reduction in incidents of colorectal cancer mortality has been the institution of guidelines for screening and surveillance colonoscopy in both normal and increased risk groups in the U.S.

These are based on the following elements. First, the national polyp study has demonstrated that 3 years after a cleansing colonoscopy with endoscopic inspection of the colorectal surface and excision of polyps at baseline, the incidents of cancer was reduced by 76 and 90 percent, compared to two reference populations.

Second, approximately 95 percent of colonoscopies performed by competent endoscopists resulted in examination of the entire colon rectum and successful removal of histopathologically advanced

pre-malignant polyps.

Finally the serious adverse event rate linked to colonoscopic examinations is between approximately .1 percent and .3 percent as we heard. This is relatively low.

The effectiveness and safety of colonoscopic screening surveillance, borne out by these observations, establish an important benchmark for other prevention modalities. Next slide.

In clinical practice, a meaningful benefit of cancer risk reduction that is linked to the administration of a chemopreventive agent, may not be achieved if there is one or more of the following.

First, poor compliance during long term chronic administration of a drug. Second, lack of sufficient duration of the treatment of patients. Third, rebound of adenomas neoplastic growth despite continued chemoprevention treatment.

And finally administration of ineffective doses or reserval of efficacy due to other concomitant medications or medical conditions. Next slide.

To address the safety analysis of chemopreventive agents, I will briefly touch on the following issues. First, the appropriate population in which an analysis of risk that includes drug

toxicity should be performed.

Second, I will point to a number of examples of drug classes which may have important chemopreventive properties, but which also may be tied to significant safety issues.

These include non-selective, non-steroidal, anti-inflammatory agents, including aspirin and COX-2 inhibitors. Finally, to sort through offsetting benefit of cancer prevention versus risk attached to treatment, the issues of power calculations and study design will be raised.

It needs to be emphasized that the targeted patient population for chemoprevention will encompass a very large segment of the geratic community, which may be especially susceptible to severe clinical manifestations of drug toxicity.

In addition, because of the high frequency of co-administration of multiple medications in this group, significant drug-drug interactions may occur. The incidents of drug related toxicity may increase after chronic administration.

An example might be drug related serious thrombotic cardiovascular events, which may be more prone to develop as a result of long term treatment. Finally, chronic treatment of with a chemopreventive

agent may slow the macroscopic appearance of adenomas polyps, but not affect progression towards dysplasia and cancer.

It is not inconceivable that individuals chronically treated with a chemopreventive agent may exhibit a higher probability of developing malignancy associated with microscopic and small adenomas lesions than non-treated subjects.

Such outcomes can only be determined by studies with long term treatment protocols. Next slide, please. Recently, a number of studies have concluded that administration of certain non-selected, non-steroidal agents, or COX-2 inhibitors, may suppress adenomas polyps and cancer.

Each of these classes of drugs are associated with potential advantages and disadvantages regarding their safety profiles. These may have a strong impact on their overall benefit as cancer prevention agents.

For example, a number of studies have suggested that the overall benefit of aspirin is strongly affected by the relatively high annual rates of serious upper-GI treatment complications, which individuals over the age of 65, may be as high as 16 per 10,000 patient years.

In the calculation of overall benefit of aspirin administration, consideration for possible concomitant prevention of cardiovascular events must also be given. In the case of COX-2 inhibitors, concern has been raised about the possibility of drug related serious cardiovascular events linked to treatment.

For example, in the Vioxx GI Clinical Outcomes Research study, commonly known as VIGOR, in which the mean duration of treatment of approximately 8,000 randomized patients was 9 months, treatment with 50 milligram doses of rofecoxib was associated with an MI rate of 74 per 10,000 patient years, compared to only 15 per 10,000 in the control naprosyn 500 milligram bid treatment group.

Regardless of whether the excess of Mis is due to toxicity of rofecoxib, or alternatively a protected effect of naprosyn, further study of such adverse drug events is essential in order to establish a benefit risk analysis in chemopreventive treatment for the elderly. Next slide.

It is expected that the context of current standards of care in the U.S. for eradication or for an indication of colorectal cancer chemoprevention, the incidence of drug associated serious adverse

events and mortality should be small enough to be overshadowed by the benefit of a chemopreventive agent related reduction and cancer-linked mortality, and/or serious complications associated with colonoscopy.

Clinical studies should be powered to adequate measure these effects. In clinical studies, the statistical power for safety end point measurements is a function of both the number of treated patients and the duration of treatment.

Therefore, cancer chemoprevention studies must contain adequate numbers of patients. An adequately powered analysis of subsets of patients is needed to ensure the number of preventive colorectal cancer cancers will exceed the number of patients who will get serious adverse events.

Remember, for indication of cancer prevention, a lot of healthy people without illness will be treated and exposed to a drug. In some instances, to maximize the safety outcomes and mortality analysis treatment of an extended duration will have to be analyzed. Next slide.

For each of the previously mentioned reasons to treat with a chemopreventive agent shown on the left side of the slide, there are distinct possible benefits as rates can be estimated.

First, we could think about adding chemoprevention to the presently recommended regime of colonoscopy as an adjunct. In this case, there would be little benefit from preventing cancers that are already prevented by colonoscopy.

The benefits should come from preventing those cancers that are missed by the procedure. Assuming colonoscopy misses precancerous lesions in one patient in four, and that all of these would develop into cancer, the rate is about 4 per 10,000 patient years, or perhaps 11 per 10,000 in higher risk patients.

Second, we might think eventually replacing the recommended regime of colonoscopy as an alternative. In this case, there would be an additional benefit of avoiding the cost, discomfort, and possible adverse consequences of the procedure.

We estimate that the serious adverse event rate for colonoscopy to be at .3 percent. So, for three colonoscopies per lifetime, and that is just a padunct figure, the adverse event rate approximates 3 per 10,000 patients.

When this possible benefit is added to the total chemoprevention benefit, it could be as high as 7 per 10,000 in normal risk, and 14 per 10,000 in

higher risk patients.

Here we are oversimplying of course counting cancers and serious adverse events as equal, and leaving out other less serious consequences of the procedure.

These two possible regimes of adding on to or replacing current practice are extremes of course. We might also imagine something in between, where patients treated with chemopreventive agents still undergo colonoscopy, but less frequently.

Thirdly, there may be a population who would comply with a regime of chemoprevention, but not colonoscopy. For such individuals, the reference therapy is nothing at all, and preventing any cancers is a benefit.

Whether it would also have been prevented by colonoscopy is irrelevant, because these individuals are not having a screening procedure. We estimate the background rate of cancer distributed between ages 40 and 80 in untreated patients is approximately 15 per 10,000 patient years, or 45 per 10,000 in higher risk patients.

As a general rule if drug related serious adverse events are above the rates of the benefits of treatment, then approval is difficult to justify.

Next slide. I want to thank Dr. Thomas Permutt, a mathematical statistician in our biometrics group, who helped us develop the next few slides.

Another way of looking at these figures is in terms of the number needed to treat. That is, as I showed you in the previous slide, if the rate of colorectal cancer is 15 in 10,000 per year in normal risk, people who altogether avoid colonoscopy, and we are able to eliminate the cancers by chemoprevention, we need to treat about 700 people for a year for each case of cancer prevented.

The number needed to treat would be a little less for higher risk groups, and a little more for prevention that was less than perfectly effective. But it still is going to be in hundreds or thousands, regardless of these variables.

This means of course that if there are any risks associated with the preventive agent, we need to expose some hundreds or thousands of people to these risks to reap the benefit in a single patient.

This is the main difference between treating a frank disease at one end of the spectrum, and preventing a rare disease at the other. In treating sick people, we may hope that therapies will be effective. If not in all patients, then perhaps in

a half, or a quarter, or a quarter, or even in ten.

Furthermore, we would be able to observe whether the therapy was effective or not and discontinue it when it was not. So the number needed to treat for many therapeutic products might even approach one.

This means that the risk of therapies largely are borne by the patients who benefit, and it can often be weighed against observable benefits for those patients.

Here in contrast the risk, if there is any, will be born principally by the hundreds of patients who do not benefit, rather than the one who does. The treated population as whole will still be better off though if the risk is not too great.

How confident can we be about how big the risk is. Well, it depends on the kind of risk we are talking about. Next slide. Consider first the possibility of rare idiosyncratic adverse events. Suppose we study 10,000 subjects for a year on a drug, and 10,000 on placebo.

And suppose we see no cases of something rare, and let's say aplastic anemia. We can be pretty confident that the risk of aplastic anemia on drug is not more than 3 in 10,000. At worse then, this risk

would be in the same order of magnitude as the benefit. Next slide.

On the other hand, suppose in the same subjects we see 100 myocardial infarctions on placebo, and 100 on the active drug. There is no evidence at all of the drug effective, but the 95 percent competency rule for difference in rates is plus or minus 14 in 10,000.

Even if we eliminated every one of the 15 cases of colorectal cancer in the 10,000 subjects that are treated with a chemopreventive agent, we would not know whether 14 of the Mis in that group are caused by the drug, or are merely part of the background rate.

Of course, if the Mis are induced by the drug, then we would be causing about one MI for every cancer prevented at a rather high price. A one year study in 10,000 patients is thus incapable of distinguishing between no harm at all and a harm that dwarfs the benefit.

In fact, to discriminate between an excess risk of 15 drug related Mis in 10,000 treated subjects from adverse events that are merely part of a background rate of one in a hundred, we would require about 70,000 patient years per treatment group.

Of course, we approve drugs all the time

without being able to confidently rule out either idiosyncratic risk or subtle changes in ordinary risks.

Again, the main difference here is the number needed to treat. Normally, we have to weigh adverse events against frequent benefits for therapeutic drugs treating active disease.

Here with a preventive drug, we have to weigh rare adverse events against benefits that are also relatively rare. Therefore, in contrast to familial adenomatous polyposis, the maximum benefit of sporadic colorectal cancer suppression is limited to a small percentage of both normal and increased risk patients who are treated with chemopreventive agents.

Since colonoscopy is effective, the benefit of adjunctive treatment is reduced when colonoscopic screening and surveillance is performed. Similarly the size of the benefit may be influenced by co-administration of drugs for other indications that would have chemopreventive properties.

An example might be low dose aspirin. A benefit risk assessment of chemopreventive agents requires accurate measurement of serious adverse events linked to the drug.

To this end, studies that are adequately

powered for safety must be performed. Critical determinants of required numbers of patients enrolled in each treatment arm are the background serious adverse event rates, and treatment duration.

In the elderly, when certain background and serious adverse event rates are high, as in the case of thrombotic cardiovascular events, very large numbers of treated patients must be analyzed.

If drug related serious adverse events increase over time and treatment studies with an adequate duration of treatment to determine cumulative adverse event rates must also be performed.

Now, what is the FDA track record for approval of chemopreventive agents so far? Based on results of the breast cancer prevention trial, which enrolled over 13,000 patients, tamoxifen has been approved by the FDA for the reduction in breast cancer incidents in high risk women.

The trial was designed with a primary objective to determine whether after five years of treatment there is a reduction in the incidence of this lesion.

The approval was linked to a 44 percent reduction in the incidence of invasive breast cancer after a median follow-up of 4.2 years. Because in the

tamoxifen treatment group of 6,500 women, there were 70 less invasive cancers in the comparable placebo group, and the number needed to treat to gain a benefit was approximately one in a hundred.

Of course, it is difficult to compare the numbers needed to treat between the tamoxifen trial and colorectal cancer prevention trials since the end point in the former case was invasive breast cancer, and there is no analogous intermediate treatment, such as colonoscopy, which can be used for breast cancer prevention.

Celeoxib has been granted accelerated approval status for the reduction of adenomas colorectal polyps in familial adenomatous as an adjunct to usual care that includes endoscopic surveillance and surgery.

Accelerated approval is considered for serious or life threatening illness when there is a meaningful therapeutic benefit over existing treatments.

Furthermore, a surrogate measure may be acceptable as a primary end point if it is likely to predict a clinical benefit. As stated in the labeling, it is not known whether there is a clinical benefit from a reduction in the number of colorectal

polyps in hereditary polypolous patients.

Or whether celecoxib treatment beyond six months is safe or effective. The approval is contingent upon performance of Phase IV studies to verify, and assess clinical benefit, and measure long term safety outcomes.

The decision of accelerated approval for this indication is taking into account the very high likelihood of the development of tumors in young patients with familial polypopous.

As I mentioned, management of hereditary polypopous patients includes prophylactic polypectomy, whose timing might be influenced by treatment with a chemopreventive agent.

So therefore it should be emphasized that both the rationale and the benefit risk analysis, which are linked to the administration of the chemopreventive agent in the management of familial adenomas polyposis patients are very different considerations that underlie treatments in the prevention of sporadic colorectal cancer.

To date, no agents have been approved by the food and drug administration for the chemoprevention of sporadic colorectal cancer. What are the essential requirements for evidence of

effectiveness and safety of agents for this indication?

How do current guidelines for colonoscopic surveillance affect these benchmarks? The agency is seeking advice from the advisory committee to address the following issues surrounding studies.

First, clarification of significance of clinical benefits linked to a chemopreventive agent.

Second, clinical design requirements that include definitions of which patients should be enrolled, the role of surrogate end points, such as adenomas polyps in measurements of clinical benefit.

The duration of treatment and adequate power for safety. These should be consistent with the specific clinical benefit that is intended. Third, data analysis requirements that include approaches to study dropouts and uncontrolled safety information.

Finally, requirements to generate a useful benefit risk analysis. Thank you.

(Applause.)

CHAIRMAN WOLFE: I am going to exercise the Chair's preoperative, and change the schedule slightly. We are 15 minutes ahead of schedule, and so while the lectures are fresh in our minds, we will open the floor now for questions regarding the various

presentations.

And I will start off while people are formulating their questions, and I would like to ask Dr. Lieberman a couple of questions. The most important complication that we have to work out with any procedure or any screening device is mortality, and you didn't mention mortality in the VA cooperative study.

I am not sure that there was any mortality, but can you discuss mortality in various series, and I have a second question for you, too, which is unrelated to mortality.

And that is how do you assess size, and how do you take into account the incredible variability among different observers with regard to the size of the polyp?

DR. LIEBERMAN: Okay. First, let me address mortality. In the published studies to date, the mortality rates have been estimated to be .001 to .003 percent, or roughly 10 percent of the rates have complications that I cited.

These deaths have been attributed to the primary complication, either the bleeding event leading to surgery and mortality that way, or a cardiopulmonary event.

In the VA study there were three deaths within 30 days of the procedure, none of which were directly attributable to the procedure. So, to answer that question. The second question, Mike, was?

CHAIRMAN WOLFE: About polyp size, because as we all know when people do an endoscopy there is a very significant different in observer estimation of the size of polyps.

DR. LIEBERMAN: I think as Dr. Levin pointed out in some of the studies that are being done right now, and in our study as well, we recognized the difficulties with estimation of size, and required some sort of quantitative measurement either at the time of the procedure itself, where a biopsy forceps is opened next to the polyp and a photograph taken, and that is what we did in the VA study.

Or there is an actual measurement once the polyp is removed prior to pathology. We don't know the accuracy of performing that latter approach, and actually we are evaluating that in the VA study right now at a couple of the sites.

CHAIRMAN WOLFE: And polyps do shrink when you cut out their blood supply.

DR. LIEBERMAN: Reportedly, they do, and although there are a couple of our investigators that

wanted to take a look at that since we have both measurements, and so we can actually look at that.

CHAIRMAN WOLFE: One last quick question. So am I to assume that if you are to recommend later on that we do look at a polyp as a surrogate that you will also recommend that polyp size be measured by some kind of open forceps, or some other equally accurate or semi-accurate measurement?

DR. LIEBERMAN: I would argue that if polyp size is going to be an important end point that you have to have some methodology for measuring it. In our study, we did -- because one of the end points of our study were adenomas greater than one centimeter, we felt that we had to have some kind of quantitative measurement.

CHAIRMAN WOLFE: And before we go on to further questions, also one last point that I do want to make, which is that Dr. Lieberman discussed other possible methods for screening, but the assumption today will be colonoscopy will be used as the gold standard, and anything else at this point is either substandard or experimental. So we will be discussing only colonoscopy today. Dr. Kramer.

DR. KRAMER: I don't know if the information or the answer to this is known, but

several, or two or three of the speakers mentioned that a particular target population for study would be those who refuse to undergo colonoscopy.

And if that is your target population, to me at least that might enter some complexities in getting the study done. For example, people who refuse one medical procedure that are "no compliers" may be non-compliers more generally.

And, secondly, I would like to know if there is information on subsequent compliance to other interventions in people who specifically colonoscopy. The second issue is when you are designing the study, to what lengths must you go to convince non-compliers?

If introduces a potential -- I don't want to say conflict of interest, but the additional complexity that if it is in your interests to get non-compliers, you have to be very careful exactly how non-compliant they are, and to what lengths you need go to convince them that they should not be in the study in the first place, and that they should have gotten a colonoscopy.

CHAIRMAN WOLFE: Dr. Kramer, that is a very important question and so important in fact that we will be discussing this in the afternoon. It is one of our specific questions, and what the committee

and the guests are charged to discuss.

So I would like to hold the answer to that question, because it really isn't for any specific person. It is a very important question, and again we will be discussing it.

Before any other questions, I should remind you all that when you do start speaking, please identify yourself. It does help in the transcripts.

DR. BARON: I have one comment and one question. My name is John Baron from Dartmouth Medical School. First, regarding polyp size. Many studies, and probably most, show that once the histology of the lesion is taken into account, size becomes much less important in consideration of its potency as a risk factor or its appropriateness as an end point.

So in somewhat more sophisticated analyses, size really diminishes in its magnitude of importance. The question that I have for Dr. Avigan is in the tamoxifen studies, you mention the benefit for breast cancer that tamoxifen brings.

I am curious, but I can't remember what the benefit or risks of tamoxifen with regard to coronary artery disease are, and in your slide immediately preceding that, you mentioned that that sort of thing is likely to be an important issue.

So I am curious whether when you considered tomoxifen that you took into account the coronary artery disease experience of the patients.

DR. HOUN: Did you want to answer this? NCI ran this.

DR. KRAMER: I can give a little bit of information. Since tamoxifen does lower lipids, the initial sense was that it might decrease cardiovascular disease, and that cholesterol was felt to be a possible surrogate for a health outcome.

It turned out that in the breast cancer prevention trial that even though lipids were lower, and cholesterol was lower, there was no difference; no decrease, but no increase in the instance of cardiovascular disease.

DR. BARON: So from the FDA's perspective then, do you believe that the possibility of a harm from tamoxifen with regard to vascular disease was ruled out in the manner that you described previously?

CHAIRMAN WOLFE: Dr. Geller would like to answer the question.

DR. GELLER: In the tamoxifen study, the age distribution of the women was lower than one would wish to see a cardiovascular benefit. So the sample size was in essence too small given the age

distribution to see a cardiovascular benefit.

DR. BARON: But I am referring to Dr. Avigan's slide, and in which he said that -- I mean, he actually imposed quite a high barrier for chemoprevention studies, implying not only does the point estimate for harm have to be obviously in a neutral or positive direction, but that the lower bound of the possible harm has to not be large.

DR. HOUN: I think that the --

DR. BARON: And I am curious, and I am just exploring this.

DR. HOUN: I think with tamoxifen, because the agent has been around for 30 years, the trial was in some sense reassuring in that the serious adverse event profile, in terms of endometrial cancer risk, DVTs, PEs, was not unexpected.

And especially in this new population, in terms of women who are cancer free at this point in time and high risk for cancer, but cancer free. I mean, it was reassuring to know.

So in terms of the data from that trial, I don't think we saw any signal to be concerned about. That is unknown from the safety profile of a drug that has been around for 30 years.

DR. AVIGAN: I would just add that two of

the other points that I tried to make was that there really is no -- just as a concept, there really is no intermediate or other intervention, except for treatment, and which makes it different.

And the endpoint in that study really was invasive cancer. Again, that's not a quantitative comparative criteria, but it is a qualitative assessment of that consideration for approval.

DR. METZ: Just one question for Dr. Rustgi and Dr. Levin, who both suggested that perhaps reduction in polyp size might be an important outcome to look at.

And Dr. Avigan raised the exact opposite point, and that perhaps a smaller polyp might be just as risky, in terms of its ultimate development, and you would need to follow these patients for an extended period of time.

Now, clearly this is one of the big questions that we are dealing with, but I was wondering if perhaps Drs. Rustgi and Levine could suggest something to the surrogate that we could actually consider, such as biomarkers that might change.

CHAIRMAN WOLFE: Before we go any further, this is a discussion for the afternoon, and I was

actually going to mention that before you raised this, because size should not be dismissed at this point. It is a point of discussion.

And Dr. Avigan is not only a gastroenterologist, but he is a pathologist also, and the point that we may be sacrificing a reduction in size for a change in the biology is a more aggressive nature.

And that has to be discussed in the afternoon, and so I would rather hold off that discussion when we have that specific question in the afternoon.

MS. COHEN: Dr. Avigan, considering a patient who comes into your office, and I am asking what is the best thing to do, and I want to know how -- and maybe this is suspect and might have polyps. But what is the best way to identify the polyp?

Secondly, if you give me a CPA, how do you know whether it is effective or not? How do I find out if it is effective? And I hate to be pragmatic, but in health insurance it might determine which treatment that I get?

DR. AVIGAN: Well, thank you for the question. I would actually defer part of it to Dr. Lieberman, because I think he did talk about the

effectiveness of colonoscopy.

But I think that as just a general principal for a gastroenterologist seeing patients, and dealing with patients where there is an uncertainty principle about whether they do or do not have a lesion lurking somewhere in their colon, and that one would not know for sure, or not with certainty not well developed unless one looked.

And essentially at this time from what we have heard, the best way to look is by colonoscopic examination. And then in addition to the examination, you have the option of the excision of the polyp.

CHAIRMAN WOLFE: Does anyone want to add anything to that?

DR. LIEBERMAN: No.

MS. COHEN: My other question was that if I took a CPA, how do you follow that, and how do you know whether it has been effective or not? What method do you use?

DR. AVIGAN: I think that is the sort of million dollar question in some respects, and the recommendation of the physician would be driven by the data of the efficacy of the drug, which is what we are prospectively talking about. That is, what are the standards of study design.

DR. KRAMER: A million dollars may be a little bit too conservative.

DR. CRYER: Byron Cryer. I have a question actually for Dr. Levine. Given that one of our principal responsibilities is to determine to what extent the reductions in these intermediate end points, such as polyps, correlates with reductions in other clinical consequences, such as colorectal cancer, and I would like to come back to a comment that you alluded to which was the effect of celecoxib, and FAP.

So we know that you were a critical investigator, and an important investigator, in the celecoxib FAP trial. And you alluded to the point that in the Phase IV experience of FAP that those investigations are ongoing.

I was wondering what you might be able to tell us specifically about reductions in colorectal cancer in that Phase IV experience.

DR. LEVIN: Thanks, Byron. That is a critical question because the FDA obviously is interested in that. To date, we don't have data yet from that experience, and it is going to take a while to accumulate that. Obviously, that will be of long term interest.

DR. FURBERG: Another question for Dr. Levin. You reviewed the ongoing secondary prevention trials, and you presented us the efficacy outcomes, and you left out the safety outcomes, and if you could summarize those, and also indicate if possible the power that you have to detect the adverse effects.

DR. LIEBERMAN: Clearly, what we are looking at is a common event in a -- or a relatively common event in a population that are asymptomatic. It is of critical importance to examine safety issues.

All the studies which I am aware of, major studies, have data safety and monitoring boards which are independent of the primary investigators, and are very well aware of the issues regarding not only gastrointestinal safety, but also cardiovascular risk.

And it is obviously too early to comment on actual data because of the incompleteness of the studies have not actually reached even the one year mark.

Most of the individuals included clearly have not, but clearly independent data safety and monitoring is vital to the future of these studies, and is being examined by these groups.

So I think that can be reassuring, but I cannot give you any data to date.

DR. FURBERG: I didn't ask for data, and you didn't really answer my question.

DR. LEVIN: Because data is not yet available.

DR. FURBERG: No, but the committee can only look at the data that you are collecting, and I want to know what data are you collecting. What is your definition of safety in the trials?

DR. LEVIN: Detailed evaluations of pre-inclusion history, as well as adverse events, both significant and not significant, are accumulated in these studies.

There is frequent investigation or interrogation with monitors, and physician -- outpatient physician data is looked at by the monitors. So I think I can be reasonably reassuring that this is an object of critical evaluation.

I would be glad to provide to you, subject to availability, and probably not today, of the forms that are being used for this kind of evaluation.

DR. FURBERG: That would be helpful. Thank you.

CHAIRMAN WOLFE: Dr. Kramer.

DR. KRAMER: So this perhaps is a corollary question, but much of what we -- and this is

Barry Kramer by the way. I wanted to direct this to Bernard Levin, and it is perhaps a follow-on to the last question.

As we are struggling all day today with whether or not we can rely on surrogates of benefit, and yet I don't know what is built into such studies for surrogates at harm.

I assume we are looking for medical harms, but that may put the downside of treatments at a disadvantage if we will only accept medical harm, but we would accept surrogates of medical benefit in order to determine the outcome of the trial.

Are there any built in surrogates of harm in any of these trials?

DR. LEVIN: I can only comment with some precision on two of the trials. The surrogates that you might expect would include biochemical markers of harm, such as blood count or biochemistry profiles, and those would be surrogates of harm that clearly are being looked at.

Certain other events would be further examined if there was any kind of clinical reason for expecting there to be an explanation for symptoms. So these individuals are followed quite closely, and are monitored for global events, as well as specific

hematological and biochemical events.

CHAIRMAN WOLFE: Dr. Lippman, did you have a comment?

DR. LIPPMAN: Yes. I would like to just get a clarification from Dr. Avigan and his presentation from the gastroenterologist in the group. When you went through the calculations, and the mathematical model, you clearly were using as a disease cancer, and talked about the benefits of that statistically.

And I guess one of the issues that we will discuss here is what is a disease, and so my question is small adenomas if you do a colonoscopy, are those not removed by polypectomy? Are they treated differently than the large ones?

DR. AVIGAN: I think that they are generally removed, and Dr. Lieberman might mention that, but I guess what the subtext of your question is, is it a adenomas disease, as opposed to a sort of pre-disease state.

And I think that actually is one of the issues that we will be dealing with in our discussion.

DR. LIPPMAN: I think it is extremely important when you look through your calculations. Clearly the IEN task force, that AACR that Dr. Levin

referred to, the whole movement in the field is that these types of lesions are diseases.

And if they are being treated surgically by polypectomy, that would sort of reemphasize that they are diseases.

DR. AVIGAN: I would just follow up and just point out again the fact that as was mentioned by Dr. Lieberman, that most adenomas do not go beyond the state of early or premalignant lesions, and that the other point about that which must be considered is that in the geriatric population, adenomas probably occur in at least half the population.

So that I think that that is a spin on whether we call it a disease or not.

DR. LIPPMAN: Right. And just one last thing on this. I do think that if you are telling me that these are treated differently by the gastroenterologist, then I think we can deal with it.

But if they are treated, and if they are removed, then until we know that we can leave them and not treat them, I think we have to deal with them as a disease.

CHAIRMAN WOLFE: David.

DR. LIEBERMAN: Let me just make a brief comment. I think that although it is very true that

most adenomas do not evolve into advanced adenomas or cancers, most GI physicians accept the polypectomy hypothesis as compelling.

And therefore most of us do when we encounter an adenoma remove it at the time of colonoscopy.

CHAIRMAN WOLFE: I don't think there is -- there is very few gastroenterologists who don't take out polyps. We see them and we take them.

DR. LIEBERMAN: That's correct.

DR. GELLER: Nancy Geller. I have a question about trial design. In the PRESAP study, I don't understand the role of the surveillance colonoscopy at year one relative to the end point.

DR. LEVIN: This was built in to determine if in fact there was significant benefit within a rapid period of time that perhaps could not have been anticipated.

This would have a significant impact on the expected outcome, and would also potentially if a very significant impact, might have some implications for subsequent management.

This was discussed extensively in the formulation of this trial. And while it is a 3 year trial, and the analysis will be done formally at the 3

year end point, the possibility, perhaps remote, that we might achieve a significant gain within a shorter period of time was one that we didn't want to overlook.

CHAIRMAN WOLFE: Dr. Fogel.

DR. FOGEL: Ron Fogel, and I have a question for Dr. Lieberman. Can you comment on the missed polyp rate at colonoscopy and the implications of that for further studies?

DR. LIEBERMAN: This is David Liberman. I cannot respond to that directly from the VA study. I can cite two other studies in which there were back to back colonoscopies performed; one from the early 1990s, and one from the later 1990s.

In both cases, small polys were commonalist, ranging anywhere from about 20 to perhaps 25 percent. Large polyps were rarely missed in both of these studies.

So I would suggest that colonoscopies are extremely accurate for detection of large, meaning greater than one centimeter, lesions. And they commonly miss small adenomas.

And going back to the previous question, I think that is one of the reasons that a lot of the prevention studies are designed with that one year

colonoscopy.

It is not only to detect an early effect, but it is also to eliminate the possibility that there were polyps missed on the first colonoscopy.

DR. LIPPMAN: Scott Lippman. I would just like to pick up another, I think, really excellent point that Dr. Avigan made in his slide, but I would like to extend it.

And he talked about the celecoxib study, and that it may not be permanent, but even a delay of the onset of these kinds of procedures would be important. And I would just like to extend that that is an excellent point to the entire field.

Clearly we would like long term studies that go on for 30 years and can delay things forever. But I think even short term intervention was a positive effect. That delays the onset of some of these neoplastic processes, and it could be of tremendous clinical benefit.

So again it is a concept that we will talk about more later, but I wouldn't just use that for the FAP argument. It applies to all of them and deals with the issue of treatment duration and benefit.

CHAIRMAN WOLFE: Just before we go any further, remember just to reinforce this, this is FDA

and not NIH, and we have to take into account the difference, and how displays will be designed, and recommendations we will be making, and how long the study can be.

Additionally, this point will be discussed later in some of the questions with regard to intervals for colonoscopy, and whether they can be changed with regard to what parameters are being followed. And Dr. Cryer was going to be next.

DR. CRYER: I actually have a follow-up question on the PRESAP study design, again for Dr. Levin. Given that one of the arms of the study is a combined use of celecoxib and aspirin, and given that aspirin a chemopreventive effect, I would ask you to look ahead to the data analysis in the arm of individuals who receive celecoxib and aspirin.

And I would ask how would you separate out the effect of one from the other, and would you anticipate that both would be necessary, both aspirin and celecoxib, in such patients for such an indication?

DR. LEVIN: We are very mindful of the fact that cardioprotective doses of aspirin are fairly ubiquitously used in the population. Hence, the reason for stratification.

We were able to based on the statistical power of the study to sort out the therapeutic effect or effectiveness of the combination of aspirin and celecoxib, versus celecoxib alone, compared to placebos.

So while I obviously do not have the information now, the possibility in my mind will exist that there are individuals, particularly in the older age groups, who will benefit from cardioprotective doses of aspirin, which may be subclinical in their benefits, in terms of prevention of adenoma reoccurrence, or colorectal cancer mortality carried out over a long period of time.

But who nevertheless may benefit from chemopreventive effects. So we will have the ability to determine that on a short term basis, and over the long term, it is conceivable to me that both types of agents, a low dose aspirin, and a chemopreventive agent, would be of benefit.

So at this point it is impossible to tell you whether we will see that, but clearly that is in the back of our minds in designing the study in that way.

CHAIRMAN WOLFE: Dr. Geller and then Dr. Goldstein, and then Dr. Camilleri.

DR. GELLER: I will begin by adding to Dr. Levin's comments, and by stratification of the study, like is compared to like, and so in the aspirin users group you are still comparing celecoxib to placebo.

But in that case, it is the additional benefit, and in the non-aspirin users -- again, it is like to like. So that by stratification, he has really taken care of that, and by looking at the subgroup separately, you can get at the end of the trial an estimate of the benefit in each group.

So then that would give the estimate of the benefit beyond aspirin, and the stratification was exactly the right thing to do to answer your question. And I wanted to ask a question about grading of adenomas. We haven't really had too much in the way of details.

So if we wanted to distinguish between those with malignant potential, and those with not, is there anything that you can tell us? And I don't even know who the question is addressed to.

DR. LIEBERMAN: This is David Lieberman, and I can make a brief comment about that. And there was earlier comments, and perhaps Anil would want to comment on this as well.

Clearly, histology is important, and we

know that there is a relationship between the severity of the histology and the mutations and genetic changes that we see in these lesions.

And therefore their likelihood to progress to malignancy. So if we move down the chain from cancer to an adenoma with high grade dysplasia, that is clearly a lesion that may progress to evasive cancer; and down to the next level of histology, which would be an adenoma with various histology.

And which seems to be in most of the studies associated with a higher risk than an adenoma that is a tubular adenoma. Size alone, as has already been alluded to, seems to be associated with risk, but very often there is a concomitant association with advanced histology. Others may want to comment on that.

DR. LEVIN: May I comment on that, please? In the studies that have been done, and so this is a practical example, all the lesions are examined, and they are taken out by polypectomy, and they are put in individual bottles, and examined by a study pathologist on-site.

They are also examined by central pathology, so that there is uniformity of decision making about the histological subclassification. And

then in doubt, a reference pathologist is used.

So I think there is some rigor about how to classify these adenomas. As I mentioned earlier, and David Lieberman has again emphasized, the size is looked on as one of the factors that needs to be taken into consideration, and perhaps as a follow-up on what John Baron said, in terms of a national polyps study, Dr. Enzaba looked at the risk ratios, odds ratios, of the findings at baseline colonoscopy.

And I am not going to give you the confidence intervals, but greater than six millimeters was associated with a 1.24 greater incidence, over one centimeter, 1.68, and an important finding of two lesions or more associated with 2.32.

CHAIRMAN WOLFE: Anil, did you want to make a comment about this?

DR. RUSTGI: I would just underscore the need for reliance on histopathology over size, and I think that practicing gastroenterologists can reenforce that. I think in terms of the correlation of histopathology with the whole spectrum of genetic alterations that remains predominantly investigational.

I would draw an analogy from a therapeutical viewpoint for Stage 2 or Duke's B colon

cancer, in which there is an effort to stratify patients with certain types of genetic alternations who might then benefit from chemotherapy.

So the hope is that histopathology can be correlated with certain genetic alternations, and then those patients can be stratified for certain types of chemopreventive approaches perhaps more effectively.

CHAIRMAN WOLFE: We are going to take a break now. We have actually go on longer than I thought, and we will come to questions after the break.

And I anticipate also that we will probably be breaking for lunch a little earlier. Therefore it is 10:32, and we will meet back here at exactly 10:45. Before we break, could all the members and the guests come forward. I want to ask a couple of quick questions of everybody.

(Whereupon, at 10:34 a.m., the meeting was recessed and resumed at 10:51 a.m.)

CHAIRMAN WOLFE: I would like to get started again, and I would like to continue with the questions. So again we will open the questions up from the members and from the invited guests, and then we will have the open forum. I think that Dr. Goldstein was next.

DR. GOLDSTEIN: This morning's discussion seemed to omit one area that I think we need to pay attention to, and that is the epidemiologic data, current data, and prospective data, of course, in the area of the safety of the currently proposed CPAs.

Each day there are a million or more epidemiologic events, such as the one that Ms. Cohen hypothesized between her and her doctor. And I think there is considerable data available on these, and I wonder if it could be made available to the members of the panel.

The current safety data and I will grant you that it is not perhaps directly related to this particular disorder for the various COX inhibitors. But I think it is something that is germane to the discussion of safety, and that data does exist.

CHAIRMAN WOLFE: It is germane. However, this is -- remember that the purpose of this meeting is not to discuss COX-2 inhibitors, nor any other specific agent.

And for that reason, we are going to discuss safety concerns during the afternoon when we discuss all the various questions that are being raised, and that are being opposed officially to us.

So with regard to specific agents, I don't

think you could get them from -- I am sure that Dr. Levin has them, and Dr. Lieberman probably has them as well. But I would like to hold that off, because again this is a generic meeting, and we are talking about drug X.

We know what class if this comes along five years from now. We never heard of it, and we never heard of the class, and how will we propose and how will we design a study, and how will we help the FDA work with the agency, with a company, to design this study. So let's hold off on that.

Actually, I think next was Dr. Camilleri.

DR. CAMILLERI: Thank you. I would like to address two issues. The first pertains to the comment made by Dr. Scott Lippman pertaining to if a gastroenterologist sees a polyp, does the gastroenterologist automatically take that polyp out, because you are using that as a means to in a way define the broad spectrum of a disease.

I would submit to you that maybe this is a minority opinion, but there are many gastroenterologists around the country who will apply a risk benefit to the individual patient.

For example, if one sees a 2 to 3 millimeter polyp in the colon on a 75 or 80 year old,

I think many gastroenterologists will apply clinical sense and look at the risk benefits, even though it is very small, of a hemorrhage or a perforation from a polypectomy using a snare.

Therefore, I think we need to more broadly look at the question that you posed, sir, in relation to does every polyp have to come out, and does every polyp require prevention. And then I would like to make a question after that general comment.

DR. LIPPMAN: That is an excellent comment, and as I thought I mentioned, I am not a gastroenterologist. I am a medical oncologist, and so I was really asking the question, because I don't know. And I think if we agree that certain polyps should not be removed, then maybe we should change the screening guidelines.

So whatever we define as something that we treat surgically with polypectomy is what we should be talking about as end points for prevention.

CHAIRMAN WOLFE: Just one second. We are talking about again prevention, and the whole idea of the 75 to 80 year olds, or 90 year olds with a polyp also pertains to using aspirin or any other drug for cardioprophylactic, and if you are going to aspirin or any other drug for a cardioprophylactic, are you going

to cardiac prophylaxis for a myocardial infarction with aspirin.

And so that is almost the same question, and so in a way let's --

DR. CAMILLERI: Well, with all due respect to the chair, I think the question pertained to defining a disease by the decision taken by a gastroenterologist to take it out. I have never been taught that that is the way you define a disease.

But I think that the other point that I would like to raise pertains to the clinical significance of the Steinbach study to which Dr. Bernie Levin referred.

And I wondered if I could ask Dr. Levin to help me as a gastroenterologist and also as somebody who is trying to advise the agency on the optimal designing of clinical trials.

What is the clinical significance of a 30 percent reduction of the number of polyps, and a 5 percent significance or reduction in the size of a polyp, which were the major changes in that model which I think serves us in today's discussion very well, because one might take the liberty of thinking about FAP as an accelerated course in the molecular events that might be pertinent to sporadic colorectal

cancer.

So I think in order to help us understand what might be the appropriate end points, could you help us interpret what it means when there is a 30 percent reduction in the number of polyps, and a five percent reduction in the size. Thank you.

DR. LEVIN: Thank you, Dr. Camilleri. Michael, the demonstration in the FAP trial of a benefit of the administration of celecoxib also was backed to some extent by a earlier study by Dr. Frank Giardiello of Sulindac, and by a significant other evidence, some of which I presented, and some of which is well known, pre-clinical, and animal, and then finally human.

So it rests on a body of evidence that is entirely consistent with the intervention. Specifically, this was a proof of principle,and it was a demonstration, perhaps for the first time, that a chemopreventive agent with probably many sites of action in the gastrointestinal tract, could have the potential for benefit.

I believe that the FDA acted wisely in saying it was a pharmacological adjunct. It did not replace surgical management and never will in that level of benefit.

It possibly allows for a delay in the timing of surgical intervention. It also opened the possibility of having a benefit in the upper gastrointestinal tract, and in a paper that is either in public press or is about to be finally published, there was also some benefit on the adenomas and the duodenum, which has even more significance, because of the unfortunately outcome of major surgical intervention in the duodenum and biliary axis.

So to answer your question in summary, I believe it was a step forward in defining what might be one of the desired end points, but in itself only leads to more questions and further studies.

DR. CRYER: This is Bryon Cryer and I have a question for Dr. Lieberman. In thinking about this issue of the potential for chemopreventive agents to increase the time interval between colonoscopies, I wonder whether you have some insight into the following, which is for X increase in interval between colonoscopies, what number of patients might that increase access to colonoscopy for based upon any of your studies or any of the data that are out there? If you could give us some guidance.

DR. LIEBERMAN: I can only give you some crude ideas about this. We currently -- well, if I

understand your question correctly, you are really dealing with resources and capacity that we have for performing a colonoscopy?

DR. CRYER: That's correct.

DR. LIEBERMAN: And the estimates that we have right now is that they are somewhere about 4-1/2 million colonoscopies performed in the United States right now. I showed you some data showing you the potential for the current indications for those.

And obviously if we can shift some of those current resources in the screening, we create more available resources for a colonoscopy. And if we can extend or can expand the interval between screening events or surveillance events, we further expand that capacity side of that equilibrium that I showed you.

I think it is possible to do both, and that is both shifting and in extending the intervals between events that are needed.

DR. CRYER: Right. So specifically I am interested in some guidance on actual time intervals and to what extent would an increase in time interval actually increase that capacity? Do we have any data that might be able to guide us in that way?

DR. LIEBERMAN: I am not personally aware

of such data. I mean, you can model that kind of data. We published -- Doug Rex and I published a small paper in Gastrointestinal Endoscopy a few months ago that outlined the potential impact of these shifts, and estimated that were we to do the shifting that I just suggested that we would probably still need an increase in capacity to offer a colonoscopy to 60 percent of the inherent population of about 750,000 new procedures.

I don't know if that answers your question or not.

CHAIRMAN WOLFE: So right now there is no hard data or there is no estimates.

DR. LIEBERMAN: There certainly are no hard data that I am aware of.

CHAIRMAN WOLFE: Dr. LaMont.

DR. LAMONT: Tom LaMont. I have a question for Bernard Levin and perhaps for Mark Avigan, and it relates to how you handle potential confounders for colorectal cancer risks, and specifically the ones that I am thinking about are folic acid, which has been shown in a big study to have a fairly impressive effect on reducing mortality, and also alcohol, which has the opposite effect.

And in a recent paper that I have seen

that has not been published yet, that it showed that in patients who don't drink much or none, and who do take supplemental folate, it had a profound effect on reduction of colorectal cancer.

So a lot of doctors already are giving patients folic acid. So I guess my question is -- and like the aspirin question that you had, how do we factor these other variables? And there is probably more than those two as well.

DR. LEVIN: In the course of obtaining the data on the patient, any medications, including over-the-counter ones, are asked about. So to the extent that most multi-vitamin preparations contain 400 micrograms a day of folic acid, we will have that information.

Of course, this is a randomized control trial. So we would hope that the events would be equally distributed, and including the ingestion of supplemental medications, such as folate, and including habits, dietary habits, such as alcohol use.

The dynamic nature of this of course is very important. It may be evolving over time, and it is something that we will need to be sure of that we are asking about in any future designs or studies, and we may need to be even more explicit than we are.

But I believe that both the design of the study and the questionnaires are addressing that to a considerable extent even currently.

CHAIRMAN WOLFE: Dr. Richter.

DR. RICHTER: Joel Richter, Cleveland. David --

David Lieberman, I think that all of us in gastroenterology feel like we are spending a lot more time on polyp surveillance when we ought to be spending more time on screening and you emphasized it.

And you emphasized in your presentation there are really recommendations for colonoscopic surveillance programs which are really based on societal opinions rather than hard data.

Is there any plan in the near future to -- my guess is probably to extend these intervals and to rationalize them more, or are we still going to be dealing with opinions, suggesting that one small tubular adenoma means that you are married to a colonoscopy every -- in some places every three years, and other places five years?

CHAIRMAN WOLFE: I am going to answer that question because we are not going to answer that question right now. That is part of our charge for the afternoon for the discussion to see whether or not

these trials may lead to an increase in the interval if it is possible to look at that question.

So again we will be looking at this in the afternoon. So I would like to now, unless there is any more pressing questions of the speakers very specifically, I would like to move on to the open forum.

And our first speaker in the open forum will be Dr. Robert Sandler, of the University of North Carolina, and I would like to remind people in the open forum to state their affiliation, and whether or not they are representing any firm or any potential conflicts they may have.

DR. SANDLER: Good morning. I am Robert Sandler, and I am a Professor of Medicine and Epidemiology at the University of North Carolina, Chapel Hill.

I am a gastroenterologist and for the past 15 years, I have been conducting studies on the epidemiology and prevention of colorectal cancer. I have been an investigator in a number of chemopreventions studies.

For example, I was an investigator in John Baron's calcium and aspirin studies, and I am an investigator in the Merck-sponsored Vioxx study, and I

am the study chair of a randomized trial using aspirin to prevent adenomas in cancer patients.

I am also a consultant to Merck, and Merck is compensating me for my time today. And what I would like to do is to to discuss some of the design considerations and implications for chemoprevention studies.

Next slide. And the way that I propose to organize my talk is to pose a series of questions that I will answer, and there is three important points that I would like you to take away from these questions.

The first is that adenomas are appropriate end points for chemoprevention studies. Secondly, that a three year interval would be a logical interval for a chemoprevention study, and most importantly that an effective chemopreventive agent would have implications as an adjunct to colonoscopy. Next slide.

So the first question is colon cancer a preventable disease, and we know that when people migrate from a low incident country, such as Japan, to a high incident country such as the United States, the rates of disease go up within one generation.

In fact, the highest rates in the world

are seen in Japanese men living in Hawaii, and that implies that there is something in the environment that is responsible for colon cancer.

In fact, experts have estimated that between 80 and 90 percent of colon cancers is caused by something in the environment, and that means that if we could figure out what it is in the environment that is responsible, we could prevent 80 to 90 percent of colon cancer.

And it is this information that underlies the concept of chemoprevention. Colon cancer is preventable. Next slide.

Well, in order to prevent colon cancer the most logical way to test an agent would be to conduct a randomized trial, and what I have done in this slide is that I have sketched the architecture for all randomized trials, and the two parts of this that I would like to discuss today are the intervention into how long should we conduct this study, and information from that might come from how quickly the agent might work, and whether there is rebound or tachyphylaxis.

And the other important point that I would like to talk about are appropriate end points. Next slide.

If we wanted to test an agent to prevent colon cancer

the most obvious end point would be colon cancer, but there are practical implications to trying to use colon cancer as an end point for a chemoprevention study.

First of all, it takes decades for colon cancer to develop, and none of us is patient to conduct a study that lasts that long. Secondly, colon cancer is relatively uncommon, which would make the sample size for a prevention trial prohibitive. And finally there are ethical complexities to using cancer as an end point.

Gastroenterologists in this country remove polyps, even small polyps, and by removing those polyps, we lower the cancer risk sufficiently so that it would be ethically impossible to use cancer as an end point. Next slide.

Well, if we can't use cancer as an end point, perhaps we could find some surrogate end point instead, and as you heard earlier this morning, in a task force from the American Association for Cancer Research, recently published a paper in the Journal of Clinical Cancer Research, in which they discussed the concept of using intraepithelial neoplasia as an important target for accelerated new agent development.

And these intraepithelial neoplasia are pre-cancerous lesions, and adenomas are one variety of IEN. Next slide.

The authors of this article concluded that IEN, and you can substitute adenoma, that IEN that is a disease, and the treatment provides clinical benefit.

They went on further to say that reducing IEM burden is an important and suitable goal for medical intervention to reduce cancer risks and that achieving

prevention and regression of IEN confers and constitutes benefit to subjects and demonstrates the effectiveness of a new treatment agent. Next slide.

What I would like to do next is to spend some time reviewing with you the information on which we could argue that adenomas are an approximate end point. Some of these points have been made earlier.

So, for example, the pathology of cancer and adenomas are similar. Adenomas are displastic lesions, and there are nuclear and cytological abnormalities that are seen in adenomas that we also see in cancer.

And sometimes when we remove a small cancer we will find a remnant of the adenoma from

which it arose. Secondly, as you have also heard, the molecular biology is similar. There are certain genetic abnormalities that we have known about for more than a decade that are found in adenomas and also found in cancer.

The experience that FAP patients is informative. Those patients universally develop cancer supporting the idea that those adenomas in the FAP patients when on to cause cancer.

And importantly there are three large trials that have important implications. So, for example, in the National Polyp Study, patients were randomized to two surveillance intervals and all polyps were removed.

And as you heard the observed number of cancers was lower than the number expected. And we could quibble about how much lower that risk was, but it is very clear from that study that removing adenomas, even small adenomas, reduce the risk of cancer.

Secondly, the Telemark study randomized people to get sigmoidoscopy or no sigmoidoscopy and followed them over time. Those with sigmoidoscopy had polyps removed, and at the conclusion of the study those who had been randomized with sigmoidoscopy were

substantially less likely to develop colorectal cancer.

And finally the Minnesota Fecal Occult Blood Testing Study randomized patients to screening with FOBT, and the screened group were less likely to get cancer and less likely to die from cancer.

So what is important here is that this body of evidence clearly demonstrates that eliminating adenomas reduces the risk of cancer.

And this is no longer a hypothesis, and this is no longer a theory. This is a fact. If we can eliminate adenomas, then we can reduce the risk for cancer. Next slide.

Now, if we can use adenomas as an end point, how quickly might we see an effect. This is a randomized study that John Baron reported in The New England Journal, and those who were randomized to the calcium group enjoyed a 19 percent decrease in the number of polyps, and a 24 percent decrease in the number of polyps.

Now, this particular study featured two colonoscopes; one colonoscopy at one year, and a second at four years. And what you can see is that as early as one year there was a statistically significant decrease in the number of polyps, and that

same risk estimate persisted at the four year interval.

Simply demonstrating that in a relatively short time, within one year, we are able to demonstrate the benefit of a particular chemopreventive agent. Next slide.

Now, if an agent decreases cancer or an adenoma risk, is there a risk of rebound, and this is a study for familial polyposis. The patients were randomized to sulindac or placebo, and the treatment continued for 9 months.

And when the treatment stopped, you can see that the number of adenomas in the sulindac group increased, but the curves are parallel. There was no evidence of rebound. Next slide.

And finally there is a concern about tachyphylaxis. In a very important paper that was published in the Journal of Gastroenterology this month that followed a group of patients with familial polyposis who were treated with sulindac long term. Next slide.

And what the study showed was that the following. This is the mean number of polyps and the percent reduction, and you can see that at the end of 12 months there was a 76 percent reduction in the

number of polyps.

And at the time of the last follow-up, which was on average 63.4 months later, there was a 74 percent decrease in polyps, and in fact 50 percent of the subjects were polyp free.

What this study suggests is that an agent that was then shown to have benefit over the short term had a long duration of benefit. Next slide.

Now, perhaps the hardest question is how long should we conduct this study. And as you have heard a multi-disciplinary group developed guidelines for surveillance colonoscopy. Next slide.

And the guidelines for patients with polyps are shown here, and so persons in whom a large or multiple adenomas polyps are found and removed, should have an examination 3 years after the initial interval.

And the interval for subsequent exams depends on the type of polyps that were detected. Based on this I would make the following arguments in support of using a three year interval for a study.

First of all, a three year interval is the current standard of clinical practice from these evidence based guidelines. Secondly, a three year interval is a decision point. We make decisions about

future colonoscopies based on what we find at three years.

Thirdly, and it is not on this slide, if we wait for 3 years, a sufficient number of events will happen so that we can statistically demonstrate a difference between groups.

And more importantly if we conduct a study for three years, patients are more likely to comply with the study. If we extend the study to 4, or 5, or 6, or 8 years, patients are likely to drop out, and their drop out will erode our ability to demonstrate an effect.

And finally, and most importantly, this three year interval is a standard that has been adopted for all of the chemoprevention studies that are currently in the field and for all the chemoprevention studies that have been finished.

So I would argue that a 3 year interval would be appropriate. Next slide. So what are the implications of all of this? Because virtually all colorectal cancers develop from adenomas, preventing adenomas will prevent cancer. Next slide.

So if we had an effective chemopreventive agent, first of all, it would supplement the benefit of colonoscopy. And I don't think that any of us are

talking about chemopreventive agents as a replacement, but rather as an adjuvant to colonoscopy.

And the reason that we need an adjuvant to colonoscopy is because we miss polyps. You have heard this morning that the mis-rate ranges between 15 and 25 percent, and that is in the best hands, and it could be higher than that, and we also miss cancers.

So the benefit of colonoscopy derives from the fact that we remove the polys that we see. And there is no benefit from the polyps that we miss. And most importantly, and this may be the most important point that I will make, is that we don't do anything to alter the underlying risk.

So taking out a polyp is like putting our finger in the dike, and it would be much more logical if we could strengthen the dike so that new leaks would not develop.

So the first benefit would be to supplement the benefits of colonoscopy. Secondly, an effective agent in theory would decrease the number of polyps, and decrease the size of the polyps.

So that when we see a polyp, we use a snare, and we use an electrocautery, and there is a little bit of smoke, and at the end you can see the cautery burn with an artery in the middle of it.

But if that doesn't hold there is a risk of bleeding, and that cautery can weaken the wall, increasing the risk of perforation. So removing large polyps is not completely safe.

If we could make the polyps smaller, then we have a safer examination. So the consequences of having an effective agent would be safer examinations, less frequent exams, and fewer cancers. Next slide.

So to answer all of the questions that have been posed at the beginning colorectal cancer is a preventable disease. Adenomas are important surrogate end point biomarkers for chemoprevention studies.

Treatment effects may be detected at one year or even sooner, and there is no evidence of rebound attack ortachphylaxis from the studies that we have available.

A three year duration is sensible based on the opinions of experts and current clinical practice, and treatment could provide benefit by increasing the screening interval, thereby decreasing the associated morbidity and lowering health care costs. Thank you.

(Applause.)

CHAIRMAN WOLFE: Dr. Sandler has the only slide presentation, I believe, and so do we have any

questions for Dr. Sandler? Yes, Dr. Lippman.

DR. LIPPMAN: Just a clarification. On the slide, you had duration of effects, and how long was the treatment interval? Was that the 9 month of treatment? Do you recall that?

DR. SANDLER: As long as they were followed. They were followed for different intervals.

DR. LIPPMAN: How long was the treatment is my question.

DR. SANDLER: The average was 63.5 months

DR. LIPPMAN: So they were treated for the entire period of time?

DR. SANDLER: They continued on treatment, and so it was a long term follow-up study of patients treated continually.

DR. RANSOHOFF: David Ransohoff. Bob, do you want to comment on -- you said that adenomas could be an end point. Do you want to comment on what type of adenomas, and do you have thoughts about small versus large, versus advanced or is it any?

The other thing is you talked a little bit about rebound, and a 3 year time horizon for studies. Do you have thoughts about whether rebound ought to be looked for after a 3 year period?

DR. SANDLER: Well, as far as the first

question, it seems to me that since we don't know which adenomas are going to go bad, that any adenoma would be an end point.

So an end point then is confirmed by a couple of pathologists would seem to be a reasonable interval. I think that one thing you could see from some of the slides that I showed was that the polyp number actually goes down so that these chemopreventive agents aren't only preventing new polyps, but they are making polyps shrink.

And I think if you have seen it effective in one year, and you continue the therapy for three years, I think you have effectively ruled out rebound.

CHAIRMAN WOLFE: Dr. Goldkind.

DR. GOLDKIND: Yes, Dr. Sandler, can you explain how a study of three years can drive or produce a data driven algorithm to extend the interval between screening when the current recommendations would be three years for particular kinds of polyps, wouldn't you need a longer study to know how you might impact that subsequent period?

DR. SANDLER: Well, I would argue without data that if you performed a three year colonoscopy and saw no polyps with some chemopreventive agent that there is evidence that no polyps have developed in a

three year interval, and it would probably be safe to extend it to five years.

Whenever you go beyond the data, you are speculating.

DR. RANSOHOFF: Well, I guess that is the point. Wouldn't you want your data to go a little bit beyond current recommendations if you want a data drive decision? Because otherwise it would continue to be speculation?

DR. SANDLER: I agree.

CHAIRMAN WOLFE: Dr. Cryer.

DR. CRYER: So, Dr. Sandler, central to your argument is the fact that prevention of adenomas prevents cancer, and as you very nicely reviewed for us the gastroenterology sulindac paper. However, one point that you didn't comment on was that there was one patient in whom polyps are reduced to zero, both at 12 months and in the long term, who subsequently developed colorectal cancer on sulindac.

So how does that observation modify your contention?

DR. SANDLER: Well, you raised a comment before, and the problem with the FAP patients is that it is not a perfect model, because every single cell in their colon is at risk, and I am not sure that the

biology that we see in FAP is exactly what we see in the patients with sporadic cancers.

So there is always the risk that you won't have complete protection and the cancer may arise, but I would point out some of the epidemiology data that Dr. Levin showed, where on balance the end stage is a class decrease the risk of cancer.

There may be the occasional breakthrough, but on balance across the population I think there would be a net benefit.

CHAIRMAN WOLFE: Dr. Furberg.

DR. FURBERG: Well, Dr. Sandler, you told us about some trials that have shown that calcium supplementation and sulindac reduce the occurrence of polyps and that that is an important outcome. Is that correct?

DR. SANDLER: Yes.

DR. FURBERG: I would like to raise an ethical issue. How can you from now on then do any placebo control trials and withhold treatment that is beneficial, and so beneficial that with sulindac that you can reduce it by two-thirds?

How can you have patients sign an informed consent and not inform them that they have an effective treatment available, and you are going to

withhold that in your design?

And this question also goes to Dr. Levin for his three trials that he is involved with, secondary prevention trials, placebo control. How is that ethically possible?

DR. SANDLER: Well, actually there are no randomized trials in sporadic cancer patients. So there is no evidence whatsoever that makes sulindac the standard of practice for the spread of cancers. There is no ethical ambiguity there whatsoever.

DR. FURBERG: We are going to be discussing this question in the afternoon with concomitant medication, and how we factor them in, or if this is indeed a question that these studies can even be done because of studies that you presented.

So that is a discussion for this afternoon. First, Dr. Metz and then Dr. Lippman.

DR. METZ: Well, Bob, thanks for that presentation. I just wanted to clarify one point. Are you suggesting that the end point for these trials should be a secondary prophylaxis and appearance of new lesions of the clearance of the colon; is that correct?

DR. SANDLER: Yes

DR. METZ: Thanks.

DR. LIPPMAN: I just would like to address Dr. Cryer's comment about the breakthrough case, and I think as Dr. Levin really nicely showed, is that we are at a place with chemoprevention now where we were with chemotherapy decades ago.

We look at single agents, and we are trying to establish evidence of activity. But one thing that we know very clearly now from very eloquent molecular studies is that there are multiple pathways to cancer, and so I think with sulindac or some of the other agents, that if we show a 30 or 40, or 50 percent reduction of that, the next direction is combinations, which Dr. Levin showed, to sort of block other pathways.

So I would not consider that a negative. I mean, I would be shocked if any of these agents were a hundred percent effective knowing how complicated and how many pathways there are to cancer.

CHAIRMAN WOLFE: Unless there are any more pressing questions, I would like to move on. Barry, do you have something?

DR. KRAMER: I have a question about end points. So if one were trying to design a trial that would allow you to lengthen the intervals of colonoscopy, what would be the end point in the trial?

What would you suggest? Would it be the reduction in the number of polyps or would it be on a per person basis? Would it be the number of people with zero polyps at the subsequent follow-up that would allow you to decrease the frequency?

How would you make those decisions, size or whatever?

CHAIRMAN WOLFE: Dr. Sandler, just make this brief, because this is again part of our discussion this afternoon.

DR. SANDLER: Number.

CHAIRMAN WOLFE: That is very brief, and very good.

DR. SANDLER: Number of polyps per patient.

CHAIRMAN WOLFE: Polyps per patient. Thank you, Dr. Sandler. Our next speaker is Ms. Sylvia Kleiman.

MS. KLEIMAN: I am going to defer to Priscilla Savary.

MS. SAVARY: Hi, I am Priscilla Savary, and I am with the Colorectal Cancer Network, and we are a patient advocate network, providing support and advocacy, and we do prevention programs with the general public.

Just on a couple of points that we felt that we wanted to make sure that were kept in mind. The background paper that we had reviewed for this meeting, I appreciate this meeting. There has been a lot of very, very good questions, and a lot of very good points made, and I do have a document to leave with you on what our points are.

We want to make sure that the general public population is well represented in the samples. As we all know frequently in clinical trials, they are largely men, and not representing the women, and the cultural differences, and the ethnicity differences.

And so this is a really important point to us; that whatever clinical trial design comes out of this that it is imperative that those things are taken into consideration, and the studies are made to represent the general public.

We do want to bring to light, or we want to make the point again about even if all we find is that it increases the time between when polyps start to grow and when they start to become cancerous.

This enlarges the window that allows us to detect the polyps, and allows us to detect early cancers. And so just increasing that window will save

an extraordinary number of lives. I think the background paper was a little too low on its percentages.

It talked about 6 percent of Americans will get colorectal cancer, and 2.6 will die of it. I am hesitant about that 2.6, because colorectal cancer is nearly 60 percent death rates right now.

The Colorectal Cancer Network would like to also note that we are not expecting this to replace colonoscopies.

This is a tool, as was pointed out by Dr. Sandler, will increase the amount of time between colonoscopies, which also allows us to screen people more appropriately with less capacity in the field.

I do hope that we will not -- that any clinical trial design will not limit the study to people who are 50 and over, because there is an increasing number of people who are showing up with no family history and they have colon cancer under the age of 50.

We have a growing database of people who fit that. It is only 600 people that we have collected now, but that is over a one year period. And out of the almost 10,000 people that we dealt with last year, 10,000 patients, 600 of them were under 50,

with no family history.

And so it is very important that the clinical trials design does not limit itself just to people 50 and over. And I thank you very much.

CHAIRMAN WOLFE: Thank you. Are there any other persons who would like to speak? I thought you deferred your comments?

MS. KLEIMAN: First we heard the professional people all morning, and then we heard Priscilla, who was very expert, and now you are going to hear from an very inexpert patient, patient advocate, who is also a representative of the Colon Cancer Network.

The point that I want to make is that at another conference, I heard about DNA testing done with a slight blood test, and another one done with --

CHAIRMAN WOLFE: Was it a stool DNA sample?

MS. KLEIMAN: Yes, the stool sample, thank you. If we could find out, and my thinking is, if you can find out with these two tests who are liable to get cancer before anything develops, and that can be done with a blood test at a very early age, then they can go right to colonoscopy to eliminate or check it. And that was my question, and I thank you.

CHAIRMAN WOLFE: Thank you very much. Any other persons? And again for those who would like to speak from the floor, I would ask the same of you that I would ask of the people on the panel, that we keep redundancies to a minimum.

Again, please identify yourself and your affiliation.

DR. HAWK: My name is Ernie Hawk, and I am the Chief of the GI Cancer Prevention Group in the Division of Cancer Prevention at the National Cancer Institute. I have no affiliations with drug companies other than working as partners and trying to develop the field.

There is a few -- I think I asked for five minutes, and I only learned that this possibility was available this morning about 3 hours ago, and so my remarks are somewhat disorganized perhaps, but I will try to organize them briefly and make five key points.

And I will speak for myself. I don't think I am a maverick within the Division of Cancer Prevention, but when asked if my reviews reflect the Institute's 5,000 or so employees, I would not go that far.

First of all, with regard to continuity of disease, I think a lot has been said about that. Dr.

Sandler very eloquently pointed out the genetic, the epidemiologic, the other relevant data that are available, both in the setting of free of intervention, as well as intervention with non-steroidal anti-inflammatories that support that concept.

And I will just point out that in addition I support that view, and in addition there are other areas of carcinogenesis, both in animal models, as well as within human models, in the context of drug development, as well as independent of drug developments, support that view as well.

And in particular the FDA has awarded its approval for agents in skin cancer treatment of actinic keratoses. So they certainly in that context, in a context where they are easily removable by surgical means, as are polyps, have approved agents for that indication.

And there are other examples as well, but I won't belabor the point. The second major point that I would make is the issue of feasibility, and highlight the issue of feasibility that was raised earlier.

I was involved in the Secretary's initiative to promote colon cancer screening last

week, and so certainly in my role at the NCI, I support both approaches. I think the point of this discussion is to try to expand options, as opposed to limit them. That is certainly how I view it.

And given the 80 to 90 million Americans that are at risk for colon cancer now, and the infeasibility frankly of doing colonoscopic screening on all of them, I would expand the options that you presented this morning, in terms of limiting it to a discussion of colonoscopy alone.

I certainly support that viewpoint, in terms of efficacy. However, there is no way that we are going to be able to screen the population effectively now using that modality alone, and so we are dependent upon using other modalities.

And as you know the penetrance of those in the population is rather low. Therefore, I think that all the points that Dr. Lieberman made, in terms of decreasing the potential for this approach, to decrease costs, and increase the efficacy of screening, lengthen surveillance intervals, and perhaps reallocate resources from surveillance back towards screening, would all be money well spent.

My third major point has to do with responding to a question from Dr. Furberg earlier this

morning about safety. In our trials, we conduct approximately 15 or so trials of this type, adenoma prevention trials, and they are funded purely with public funds, as well as some collaboratively with industry.

I will say that the industry collaborative trials at least meet and in most cases exceed the safety parameters that the public funds are able to support in any of these trials.

That is appropriate because many of those agents have increased risks associated with them as well. But the sort of monitoring that is going on in the co-funded studies, where we are working closely with a collaborative partner, involve things such as every 6 to 12 week phone calls from study nurses to patients, specifically soliciting information on a range of toxicities.

And so I think while the trials aren't designed to show benefits, in terms of reducing or improving the safety, clearly we are developing data in the most rigorous manner possible in order to answer those questions in the context I think of these trials.

Next, I want to point out that colonoscopy, which we pretty much all agree upon as

being a very effective strategy, both for screening, as well as intervention, would not meet in some ways in my view the criteria that are being imposed upon chemoprevention, perhaps that is appropriate because the risks are not as great as well.

But there are no data as was pointed out earlier for randomized controlled trials. We sponsored a meeting last year of international experts that felt that was an infeasible approach to show reductions in cancer instance, or cancer mortality in a randomized controlled screening trial.

So I think the day when that is possible is gone. I personally welcome that, because I think the feasibility and importance of colonoscopic screening is obvious.

So again the point is that I would not want to enter into a scenario where we are creating a higher standard than we have for our current standard of care.

And then finally I wanted to address the issue of the developmental pathway, which we are here to try to elaborate and fill out in terms of details. Our approach at the NCI has been guided obviously by investigator initiated opportunities, but also by directed contracts arising from the NCI.

The approach that we have taken to this is solicit input from active physicians working in the field, as well as patient care groups, including the Colon Cancer Alliance, the Hereditary Colorectal Cancer Association, in the design of our trials.

And in putting all of that together, we have come up with a body of trials that Dr. Levin elaborated for you, not exhaustive, but at least some of the examples, in terms of the one year and two year end point, and that short of thing.

So at the time when the time when the trials were initiated, those represented what we felt were the best current standards for the field. That being said, you will notice that many of them were allocated as Phase III trials.

Well, since there is no approved data, we don't know what Phase III is in many regards. We have been doing what we feel are Phase III trials, but based on adenoma end points. But I guess that is the point of this meeting, is to decide definitively.

But we do feel that the involvement of the FDA in this process is welcome and important. This field will develop. Chemoprevention will develop with or without regulatory oversight, and drug approvals, and that sort of thing.

It will develop slower and based predominantly on public funding in the absence of a developmental path that might lead to "drug approvals" for new agents.

And it will do so probably less well in my view than it will with the FDA's active participation in that process. And so I am hoping that we get to the point where we can all agree upon a process that allows for FDA oversight and approval, and yet sustains the ability to do the sort of research, and to attract, but private as well as public, dollars. That's it and thank you.

CHAIRMAN WOLFE: Thank you. Any other comments? Yes, Dr. Gordon.

DR. GORDON: Hi, I am Gary Gordon and I am a medical oncologist, who has an interest in cancer prevention. I am a former employee of Pharmacia and Searle.

So in that sense, I have worked for a pharmaceutical company that has interests in this area. I have also served as co-chair of the task force that you have heard about this morning, the American Association of Cancer Research Task Force on the Prevention and Treatment of Intraepithelial Neoplasias.

And I just wanted to again thank the committee for embarking on this, because I think it is an important discussion to have to move this field forward, both from the AACR point of view, as well as the industry point of view.

And I don't want to belabor the points that have been made by others here, but clearly the findings of the task force were that intraepithelial neoplasias is a process that disease evolves from normal tissue through intraepithelial neoplasias to cancer.

That adenomas are on that causal pathway to colorectal cancer, and that as we have heard by several speakers this morning that by affecting adenomas that one can reduce the risk of cancer.

And in fact the task force was more specific in their recommendations, saying that a 30 percent reduction in the number of adenomas would be significant.

I think to address some of the comments that Dr. Avigan made this morning, I don't think the task force in any way viewed the development of chemopreventive agents or agents that would treat or prevent intraepithelial neoplasias as only having one or two outcomes; either as adjuncts, or to supplant.

But rather viewed it more as an evolutionary process, where perhaps initially it would be in conjunction with current methods for screening, and then evolve to potentially increasing screening intervals, or even potentially if the agents were effective enough to reduce the need for those sorts of procedures. And that will conclude my remarks.

CHAIRMAN WOLFE: Thank you, Dr. Gordon. Any other comments from the public?

DR. KELLOFF: I am Gary Kelloff, and I am at the Cancer Institute, and I ran the chemoprevention branch of the NCI for 10 years, and for the last year I have been in the Division of Cancer Treatment and Diagnosis.

I have served on advisory committees for industry, including Pharmacia, Novartis, and Ilex. I am not here on their behalf, nor am I retained today for this activity.

I am here out of my long interest in chemoprevention drug development, and I don't want to reiterate a lot of the excellent points that have already been made by Dr. Levin, and Dr. Sandler, and Dr. Hawk, and Dr. Gordon.

There are a few things that I think though I would like to mention. We have heard attention

between screening and drug intervention. I really think that in the setting that we find chemoprevention drug development that none of us that have been thinking about this for a long time are in any way advocating that one would be an alternative to the other.

In fact, all of the trial designs that any of us have been involved in designing and entertaining have it within the setting of colonoscopy, or the standard of colonoscopy follow-up has not been changed.

So that we could have a standard of care as the background and get new information that would give us the scientific data that we are all looking for to support development of these efficacious drugs.

So I don't see it as attention or an alternative. As a matter of fact, I believe that if chemoprevention drugs are approved and have a label out there that you would find all of those people, that is, the 85 percent that need colonoscopy that are not getting it, would be reading labels and would be realizing that something needs to be -- that they need to be doing more about their own self-help, and to be seeking that kind of care.

I think that the fact that we have an

effective screening procedure is diluted by the fact that we still have 130,000 colon cancers in the U.S., and 55,000 cancer deaths, and only 15 percent compliant users, and 20 percent miss-rates.

And that says to us that more needs to be done, and all of us have a first dictum of first do no harm. That is what we walk around thinking about in the medical procession.

But sometimes more harm is done from non-proactive action, and that cues up what is needed for drugs and certainly I applaud the FDA today and the four colleagues that are here, in terms of taking up this hard issue, and having some very key questions to chew on this afternoon.

I think on the safety efficacy equation, I think on the efficacy side that we have not seen anything more compelling for disease prevention than the setting of colon cancer. And as our colleagues said, this is not about the generality of chemoprevention, but it is about colon.

But make no mistake. Colon cancer and the scientific rationale is strongest for this target organ than any, and you have heard the eloquent presentation of molecular mechanisms of genetic progression, a la Vogelstein, of the extensive

epidemiology of 15 years or so with some of the agents.

And the animal efficacy, and although we all take this with a grain of salt as we approve clinical agents for clinical use, the animal models are getting better and better, and the genes that cause human cancer are in these animals.

You can stop these intervention trials at the polyp end points, and they go away, or you can keep the animals going, and they don't have invasive colon cancer.

And then we are already in the clinical intervention trials for the germ line lesions. They are very high risk and high penetrant cohorts, and about 85 percent or so are sporadic adenomas and sporadic colon cancer, and have the same APC gene mutated.

So we feel that the compelling efficacy is out there, and that as the trials come in that efficacy is not going to be a question relative to the polyp end point.

And one says then, well, is the polyp end point an effective and adequate surrogate. Our position, and I co-chaired the task force at AACR, and that document that you have there today, is that polyp

is first a disease because our subspecialists, all of you around the table are treating it as a disease because you take it out when you see it.

And therefore we always think of cancer as this bleeding mass in emergency. We should not have our thinking altered by the fact that it is the cancer end point that we are not so necessarily worried about here if we have a disease that needs treatment before the cancer end point.

We also have very strong evidence that you really don't get invasive cancer unless it goes through a polyp intermediate, and that is true for 85 or 90 percent of the polyp that you can see.

And I suspect that most of the rest are flat mucosa with this displastic nuclide that don't pouch up as a polyp, but if you had a biopsy, you would find the generality of this phenomenon to be probably very, very compelling, and very few exceptions.

We always have the situation that not all polyps go to cancer. We all realize that, and that is true of every epithelial sheet that humans have at cancer risk, and epithelial accounts for 80 or 85 percent of the cancer burden.

And in this document, you have not only

looked at polyp as the prototype, but high-grade PIN, cervical intraepithelial neoplasia, and down the line the nine target organs.

The science is there, and the precancerous lesion is a disease that needs treatment and is being treated. It is an obligate precursor to evasive disease, and it is the highest risk factor that we can find in these people other than rare germ line lesions.

So we think from an efficacy side that it is not a question. From a safety side, we believe that as long as the trials are put in the context of standard care, and all of the care is given with colonoscopy screening; that is, the standard of care out there, that as drugs go forward, and as approvals are gone, and as labeling is put forward, that it should be in the standard of care with colonoscopic screening, with really no change in that.

It really gets down to the chronic safety database of the drugs, and that is where the safety risk is, and that will be a subject of a lot of discussion this afternoon.

The only last question that I would pose, and I commend Mark for an excellent overview, is the number that stuck with me, which is that you have to

treat 700 to prevent one cancer, and I asked him during the break the assumptions, and this is a subject for this afternoon.

But I suspect that if you look at the people that would be prescribed or approved to get a drug under a labeling approval, that I would ask the question another way.

If you took all people with a one centimeter polyp, whether on a stock or a sessile polyp and ignore grade, does that number from 700 to 1 go down? It goes down to probably less than a hundred to one I would guess, but I don't know what that number is.

So the last question I would ask is if you take out an adenoma that is a polyp, and you have a risk of 30 percent of getting another one, are you a healthy person, because absent invasive bleeding masses and cancer, people have treated themselves and the doctors have treated them, except for the enlightened ones that are taking these lesions out as healthy people.

And I suggest that they are not healthy, and that using these precancerous lesions as end points ought to be of paradigm and prototype to move the field ahead. Thank you.

CHAIRMAN WOLFE: Thank you. Any other comments from the public? Before we break for lunch, just a couple of comments.

It is 11:45 and we will meet back here promptly at 12:45, and the other is that there is a table downstairs reserved for panelists. So we should proceed directly down there. And again we will begin again promptly at 12:45. Thank you.

(Whereupon, at 11:49 a.m., a lunch recess was taken.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:57 p.m.)

CHAIRMAN WOLFE: Would Dr. Avigan please introduce the questions for the afternoon. For the members of the panel, the questions are in your packet, but they will also be on the screen on an individual basis.

DR. AVIGAN: Okay. I am just going to read the questions as they are written, and with no commentary. Thank you. For individuals who are able and willing to undergo colonoscopic screening or surveillance, is either partial and/or complete suppression of colorectal adenomatous polyp a clinically meaningful benefit. Why or why not?

And if adenomatous polyp suppression is not a clinically meaningful benefit, what additional information would be needed to demonstrate that partial or complete suppression of polyps is of clinical benefit in such individuals.

Question Number 2. A chemopreventive agent that suppresses polyp growth may in theory cause polys to become resistant to drug effects. Additionally, it may preferentially allow small invasive lesions to go undetected on colonoscopy, while large indolent lesions are identified and

removed.

If polyp suppression is used as an end point in the clinical trials of a chemopreventive agent, (a) how long should the trial be.

(b) what should the time interval be between colonoscopic evaluations;

(c) what end points and follow-up are needed to rule out possible resistance to drug effects, differential identification, and removal of large indolent lesions;

(d) how should a rebound withdrawal effect be studied.

Question Number 3. Given that mortality and invasive colorectal cancer incidents rates are gold standards for demonstrating clinical benefit, what is the relative importance of other study end-points in clinical trials of chemopreventive agents such as (a) length and interval between, or replacement of colonoscopic screening or surveillance.

(b) reduction in the number of procedural complications; and (c), other clinically meaningful outcomes.

Question Number 4. Should the results of clinical trials and individuals at high risk for colorectal cancer be generalized to individuals at

normal risk for colorectal cancer. Why or why not.

Please specify the criteria that should be used to classify risk in clinical trials of chemopreventive agents.

Question Numer 5. Should clinical trials of chemopreventive agents be required to include substantial numbers of individuals with particular demographic or baseline characteristics, such as age, race, and sex; or on particular concomitant therapies, such as nonsteroidal, anti-inflammatory agents?

Question Number 6. In randomized placebo controlled clinical trials of chemopreventive agents used as an adjunct to colonoscopic screening or surveillance, what would represent a clinically meaningful effect size for (a) reduction of benign adenomas;

(b) reduction of premalignant lesions; (c) reduction of colorectal cancer; (d) increase in the time interval between colonoscopies; and (e), reduction of complications.

Question Number 7. How should drop-outs and censored patients be analyzed.

Question Number 8. What is your advice concerning the safety evaluation of a drug proposed as a chemopreventive agent in an at-risk population

without active disease.

And Question Number 9, the final question, for partial or complete suppression of adenomatous polyps, (a) should the proportion of the patients who experience the clinically meaningful benefit of polyp suppression exceed the proportion of patients who experience serious adverse events;

(b) if yes, should the study be powered accordingly; why or why not; and finally, (c) in order to ensure long term safety of chemopreventive agents, what should the length of the clinical trials be.

CHAIRMAN WOLFE: Thank you, Mark. Dr. Raczkowski.

DR. RACZKOWSKI: I will keep my comments very brief. I think you can see by the questions and the breadth of the questions some of the areas that we are interested in pursuing.

And as I mentioned this morning, we are primarily interested in some practical advance on the specifics of clinical trials, such as the end points, and how big an effect size would be considered clinically meaningful, study populations, issues of analysis, and how to evaluate safety. And with that, we welcome your input.

CHAIRMAN WOLFE: Before we get started, I

looked at these questions yesterday, and I grouped them in a slightly different order because of the relationship of some of the questions to the others.

So we will start with number one, and then we will go to number six, and then it will be three, two, four, five, seven, eight, nine. So it is just slightly out of order, but I think 1 and 6 are very closely related, and I thought 3 should come before 2.

And again I will read the question before and then I will call on specific people to start the discussion, and again I urge you to say what you need to say, but again keep redundancy to a minimum.

So the first question is that for individuals who are able and willing to undergo colonoscopic screening or surveillance, is either partial and/or complete suppression of colorectal adenomatous polyps a clinically meaningfully benefit; why or why not.

If adenomatous polyp suppression is not a clinically meaningful benefit, what additional information would be needed to demonstrate that a partial or complete suppression of polyps is a clinical benefit in such individuals. I would like to call on Dr. Ransohoff to start the discussion.

DR. RANSOHOFF: Well, I think some of the

considerations in looking at this question are -- and just to answer this literally -- that if you had complete suppression of all polyps forever, that is a no-brainer, and you really would have some important information if that happened, because we think that cancers come from polyps.

From what we know, however, any intervention will produce suppression of some polyps at best, and I think the kind of information that would be useful to me, or that we ought to consider if you just get partial suppression is do we look at all polyps as an outcome, or do we need to look at size, or other things that make the surrogate more proximate to the outcome, which is really one of the themes of the whole discussion.

In my view, I think that large polyps are arguably more important than small polyps, and for outcomes ought to be focused on, and again this is just a starting place for discussion.

But the reason for doing that -- there is two reasons. One is that we know something about the natural history of large polyps. It is not a lot, but we know something.

The Stryker study in 1987 that looked at lesions seen at barium enema that were not intervened

on, showed a rate of about 1 percent to become cancerous. It is the natural large lesions.

We don't even known the histology of those, but that is some of the little natural history that we have, that large lesions do bad things over time. So we know more about their natural history than we do about small polyps.

For most small polyps, because of all of the things that have been said, we know that they can't -- that most of them don't progress. The other thing is that if we use small polyps as an outcome, we have the problem of missing polyps being seen at one year or three years, which introduces noise.

One last comment before I stop is that another

-- I think that a case can be made to use advanced neoplasms as an outcome. It is something that David has used in his study, and Tom Imperiale used in his study.

But the reason that we use advanced neoplasm as a surrogate outcome is that it is more common than cancer, which is really the outcome that we want to find.

And I think even in thinking about advanced neoplasms, and we have talked about them

today as though they are evil actors. We really do not have any descriptive data identifying their natural history. And I think I will stop.

CHAIRMAN WOLFE: Dr. Metz.

DR. METZ: Thank you. I would agree with what was said before. Unfortunately, I think we are stuck with the standard of care here, and that we have to do secondary prevention trials.

And in the real world, we can't leave a polyp in, and I agree that the larger polyps are the concerning ones. So I am not going to retract what I have said before, except to agree with Dr. Raczkowski.

But I would suggest that because of that, I think we need to have a longer interval, because I am not so sure that if I find a three millimeter polyp pitch up, even if we have a one year screening colonoscopy to make sure that nothing was missed early.

But if you have a 3 millimeter polyp pitch up at 3 years is that going to be of real relevance. If you have a 5 millimeter, or a 7 millimeter, or 9 millimeter, the big lesions are the ones that would be concerning to me.

So I would be concerned that we at least have a longer follow-up if we are going to use a

surrogate end point like this. And I think I will leave it at that.

CHAIRMAN WOLFE: I am going to make some comments myself, and we will open it up for everybody else, but I said not to be redundant, but I am going to have to be redundant to some extent.

Please keep in mind again that this is FDA, and so we have to keep in mind that there is going to be a commercial interest in some regard, and we have to keep that in mind when we talk about designing or helping to design trials, or give advice regarding the design of a trial.

So there has to be a time limit of some sort, and we have to pick parameters and here the question being asked is an entire reduction necessary, or elimination necessary or reduction okay?

My comments that I am going to make is that a polyp, and which has been said, and I am just going to reiterate it, is a neoplasm. It is a new growth. It is abnormal.

And we don't know what any of these agents will do to the biological behavior. We know that size is probably the most important determinant whether a neoplasm will become malignant or not. It is not the only determinant.

And so I think in my view this question is that is complete elimination necessary? I don't think so. The reduction I think is very important. I think in a trial like this, because it is a trial, it needs to be removed.

And it needs to be examined for its mitotic index, and for any other pathological indices which would be deemed appropriate for this type of study.

DR. RANSOHOFF: If we are looking for practical things, Bob Sandler showed that after 3 years, after 1 year and 3 years, you can find reduction.

And I would ask if you can find that, and if you find no rebound for some period after that, would that be one appropriate kind of outcome to consider? Would that be helpful to people in thinking about time frames?

DR. LIPPMAN: I think related to that comment, and picking up on your point, since we really don't know enough about -- I mean, size is important, but some small lesions are biologically aggressive.

That the initial studies need to be -- well, I would think that they would need to be more broad-based, unless the gastroenterologists around the

room can tell me what size polyp they feel comfortable watching and not removing.

And until we get to that point, I think we need to do the studies more broad based, and we need to include studies of histology and biology on the resected polyps so that we can answer these questions about how aggressive the polyps are that we are removing and so on.

CHAIRMAN WOLFE: I will make one comment. We had a little discussion, Dr. Camilleri and I did, and those things that are a hundred percent or zero percent. Of course, I am not going to take out a polyp from someone who is sick and has a systemic illness, and would be at risk for taking out a small polyp.

I am not sure I would do a colonosopy on that person either though. So, in general, however, I think we will all agree that in general when we see a polyp, we take it out.

Yes, there are circumstances where we are not going to, but in most cases, we will. Now, if I am wrong, and if that is the wrong assumption, please say that. But for most, they probably will, and besides that for a trial we would.

I think for a trial this is different. We

are talking about again looking at the number, size, and the biological behavior.

DR. METZ: I think the reason to potentially go a little longer than three years is that it just gives you one point in time. I think that a one year colonoscopy, although it might give you some information, is really primarily being done to make sure that nothing was missed at the first colonoscopy.

And I don't think you can base anything on your one year data. If you could see a trend that goes from time baseline to time 3 years, to the next scope, which I am not saying necessarily needs to be 6, 7, or 8, or maybe 5 is fine, or maybe 4 is fine, and you can show a trend, then I think that would be strong information.

And it would also answer the question of tolerance and the question of rebound that has been brought up.

CHAIRMAN WOLFE: Let's stick to the question, which was one of the reasons that I picked number 6 after number 1, because question 6 addresses time interval.

So let's stick to number one for now, and we will take that into consideration for number six.

Barry.

DR. KRAMER: I am hearing some implicit assumptions, and I just want to be sure that they are more explicit. So if we decide that it is the proportion of polyps that counts, and not disappearance of polyps, then obviously we are treating each individual polyp, as opposed to individual patients.

We have changed the unit of end point, although as I pointed out before, we may not necessarily be changing the unit of toxicity, because it is the patient and not the individual polyp that experiences the toxicity.

But having done that, what polyps go into the denominator? For example, flat or depressed adenomas, would they be part of the number that is counted? If so, can we accurately identify them?

Do we know their natural history well enough to count them as part of a trial, or is it only big polyps?

CHAIRMAN WOLFE: Before you go any further, we are not supposed to do much in the way of voting here, but I think there is one aspect that needs to be clarified right now.

Again, we are talking about trials, and

not clinical practice. In a trial would anybody leave a polyp in, or should all polyps come out? Again, does anybody here think that we can just look at them and not take them out?

So we are all saying that all -- I'm sorry, but are you saying that they can all stay in?

DR. BARON: Well, there are trials that have been conducted in which there are disappearance studies that both have been done before. I think it is plausible that some could be done in the future.

They are done on smaller polyps, but to make a blanket statement that you would leave them in or wouldn't, I think that may be misleading, Mr. Chairman.

I would recommend that you define the type of trial that you are doing when you pose the question.

CHAIRMAN WOLFE: The question that we are discussing today is chemoprevention. If we are talking about preventing polyps from occurring, then the --

DR. BARON: But there are chemoprevention polyp disappearance studies.

CHAIRMAN WOLFE: But that's treatment. Once you see a polyp and you think it is disappearing

or it is going away, that's treatment. It is not prevention.

DR. BARON: Yes, but for example, in Norway there were studies where some polyps were left in, and they looked for both the regression of the existing polyps, and the occurrence of new polyps.

The other issue related to this is that I think we are making a false distinction between the event of having a polyp and the condition is something that Dr. Sandler referred to.

The thing that we are really treating is carcinogenesis. The carcinogenesis is manifest because of raised lesions, flat lesions which are suspicious for other reasons, or potentially in some of our studies -- in some of our studies I found adenomas in random biopsies, adenomatous tissue.

And so the idea of an end point in these studies needs to be broadened to include anything taken out of the bowel of the patients. Endoscopists will occasionally take a bite of something that just looks funny, and it is not a polyp, and it is not a raised excrescence.

But it is something that needs to be taken into account, and so I think the terms of your questions are very important as you pose them in order

to get meaningful answers.

CHAIRMAN WOLFE: So you are saying that any neoplasia, any new growth, should be taken out?

DR. BARON: In the conventional chemopreventive study, for secondary prevention the colon is cleaned, and then new polyps are looked for. There are versions of chemopreventive studies in which polyps may be left in place, and these are unknown histology, and raised mucosal lesions.

And then after a period of time they are removed, and that is a legitimate design, with the goal of investigating polyp regression.

CHAIRMAN WOLFE: Dr. Goldstein.

DR. GOLDSTEIN: Given the trend of the discussion so far, I would think there would be a very significant problem with ethics committees in that kind of situation.

And that kind of problem not only would affect recruitment, but the -- shall I say the interest in actually going ahead with a study that allowed that to happen, and I think you would have a problem.

DR. RANSOHOFF: David Ransohoff. I am not sure exactly where the conversation is going, but I think we ought to be careful not to give too much life

or power to small polyps, and more than they deserve.

The reason that we take small polyps out when we are there is because the patient has been prepped, and the patient has been sedated, and we are there, and they are relatively easy to take out.

There may be some circumstances where we don't, but if we were serious about treating small polyps in the United States, we would be recommending colonoscopy on everybody, and for that reason we don't do that.

And so although polypectomy is surgery, I have never thought about what we do as being surgery as eloquent as that. I don't think that makes it a disease, and I think we really have to keep in perspective that just because we take something out and treat it doesn't mean that it is important. We are doing it for a variety of reasons.

CHAIRMAN WOLFE: Please, again remember what we are talking about. We are talking about in a trial. Are we taking them out for the purpose of a trial, and for designing a trial. That is what we are talking about.

We are not talking about what we do in clinical practice.

DR. FOGEL: Mr. Chairman, I have a

question about the patient population that we are talking about. Are we talking about individuals who have had a polyp and then entered the study, and so this is a prevention of secondary polyps?

Or are we looking at a population that is at average risk, and has never had a polyp, and presents for this screening study? I think the answer to that will impact what we say.

CHAIRMAN WOLFE: That is actually not one of the questions specifically I don't think, Mark, because we are looking at where a person who has had a polyp is not an average risk. They are a high risk.

DR. RACZKOWSKI: Well, I think we are interested hearing about the patient populations that would be appropriate, and there is a question about patient populations.

I think the intent of this question really is just to get people's input on whether a polyp in and of itself is considered -- the removal of that is considered clinically meaningful, and is it simply the proportion of polyps that are removed in a patient, or in a given patient should that person be polyp free?

In other words, if a patient had three polyps and you removed one, is that a clinical benefit, or would you expect a clinical benefit to be

manifest by removal of all of the polyps in that particular patient, or prevented in that particular patient.

CHAIRMAN WOLFE: Dr. Kramer.

DR. KRAMER: That comment helps me focus my question, because as it is written, it says that you are asking what would constitute a clinically meaningful benefit.

So to help me answer that, I would like to know from the gastroenterologists if you were confident that an intervention, after you cleaned -- and taking from what you said, Mike, you clean the colon completely.

If you were confident that you could decrease the number of polyps in each person by 20 percent or 30 percent, but nevertheless every person still showed up with a polyp, would that allow you to confer at least one clinical benefit?

That is, delay your endoscopy by some period of time. I would like to know the answer to that. If you knew that instead of five polyps would come back, three would come back, would you delay your endoscopy by an additional period of time?

CHAIRMAN WOLFE: I personally wouldn't. Joe.

DR. RICHTER: No, I think the only end point if you are talking about the issue of being able to do this secondary thing, and extend your endoscopic surveillance and save money that way, because you are going to spend money one way to hopefully save in the other way.

And it is only going to be that you eradicate the polyps. Anything else is really -- there still would be a surveillance program, unless maybe you did the situation that David is talking about, and study that subset of patients who have more higher profile polyps.

That is, large polyps, one sonometer or more, that have a tubulovillous component, and then when you are looking at 3 years or at 5 years, you find that there is only small polyps, and a decreasing number of polyps, and those only have a tubular form, that might be important.

But unless you eradicate the polyps so that you don't see anything, I don't think any gastroenterologist would be comfortable of extending the surveillance program.

CHAIRMAN WOLFE: Dr. Lippman first.

DR. LIPPMAN: Yes. I will give you the short answer to 3(a) on this. I think the issue of

increasing the intervals that we are talking about here is really not on the table, certainly not at this point in my view.

I mean, that has to be shown. I mean, once you establish some efficacy of the agent, then you could do a study to see if changing the interval has an effect. I think the issue here, and that's why I keep hitting this issue of what would you feel comfortable leaving, is that if polyps are removed, for whatever reason when you are in there, I am presuming that the gastroenterologist feels that they are doing some benefit to that person, and not just because they are there.

Now, if I am wrong, correct me, because there is toxicity to that, and there is expense to that, and there is a lot of issues to do this. So I guess what I am trying to get at is if polyps are something that we feel or the gastroenterologist feels needs to be treated, and you have an agent that decreases polyps 50 percent.

And so instead of 10 every 3 years, they are getting 5, removing 5 less polyps, is that of any benefit to someone, in terms of potential adverse complications, or costs, or others.

DR. METZ: Can I respond to that? I think

the issue not so much is that you are going to have five chances of closing a perforation or a bleed, as opposed to 10 chances. I am not looking at it in that sense.

What I am saying though is that if 3 years down the pike after you run the agent, you find fewer polyps of smaller size, that to me suggests that you are making an impact on the ultimate outcome.

I would not stretch out my surveillance until the next few studies have been done to show me that in fact that does translate into a better outcome.

DR. LIPPMAN: I agree completely, and that's why the issue of increasing intervals in surveillance is a third or fourth generation study, and that has to be studied separately.

I would not feel comfortable based on activity in a trial like this doing that, but again if you decrease in number, you are decreasing the size, and presumably you are decreasing the potential complication and cost to the patient, and that is what I am trying to clarify.

CHAIRMAN WOLFE: It actually could be the same study if the study is extended. If the study is extended, and it is like two colonoscopies, 3 and 5

years, and you see that is how the original study was done, was to go from 1 to 3 years weren't they? Dr. Ransohoff, weren't you involved in those studies?

DR. RANSOHOFF: No, I think you are probably talking about the National Polyp Study, and they just did prolonged follow-up to make the first decision about extending --

CHAIRMAN WOLFE: That's what I am saying, about a prolonged follow-up and you see that one did not have any benefit over three. Isn't that the way that it was done?

DR. RANSOHOFF: That was a clinical trial to look at one and three, and they found no difference between either group.

CHAIRMAN WOLFE: So if a study is done here with a chemopreventive agent, and there is no advantage doing 3 over 5, for example, then that would provide evidence that you could potentially in the same trial -- well, that is one of the next questions.

DR. RANSOHOFF: But wouldn't you need to -- just so that I can understand. Wouldn't you need to have a study that one arm was designed with the active agent and long interval and the other arm was a standard interval?

I mean, wouldn't you need to do that study

to really answer that question? And I don't know how that could be done within the studies that we are talking about.

CHAIRMAN WOLFE: Dr. Goldstein.

DR. GOLDSTEIN: A quick comment. Not only would it be interesting to see the reaction of ethics committees, but I can only imagine the agonies of writing an informed consent form which says something like we may leave a polyp in. Or two.

CHAIRMAN WOLFE: Dr. Furberg.

DR. FURBERG: I think the question has broader implications. It is very difficult from a design point of view to just look at efficacy. You really need to weigh efficacy versus safety.

If you lower the bar, and you can claim success, and if you reduce a frequency of polys just by a tiny bit, the trials that you are going to do will involve just a few hundred patients followed for a couple of years, which is inadequate for a safety evaluation.

So you really need to weigh the two and set the bar a little bit higher, and so you get good safety information, which is equally important.

CHAIRMAN WOLFE: Ms. Roach.

MS. ROACH: When I was thinking about the

informed consent myself, and there is information in the packet that talked about the impact of the chemoprevention agents on polyp development that sometimes led to flat lesions, or smaller polyps.

And if I was reading something like that, and it said, well, we are really looking for big polyps and we are giving you something that will make the big polyps maybe be smaller, but we are not that worried about small polyps.

This is just this inherent contradiction that I don't think is going to be very clear to people.

CHAIRMAN WOLFE: Dr. Baron.

DR. BARON: Yes, I would like to sort of make the conversation a little more practical, in the context of trials. In these studies, in the National Polyp Study, or any of the chemoprevention trials that have been described here, all the end point polyps are small.

The median size of the end point polyp is 3 millimeters, 3 or 4 millimeters. There is a practicality issue that is quite serious if the only end point of relevance is defined as a polyp of, say, over one centimeter.

In these populations under colonoscopic

surveillance, they are very, very uncommon. That may or may not be a problem. I think it is not a problem because of what I said earlier, that histology really dominates size.

And that really needs to be kept in front of us as we go ahead. There is practical experience in several chemoprevention trials regarding what histology means in the context of these interventions.

So in the studies that we have done that have shown positive benefit, and that is aspirin and calcium, we have found that the benefit is roughly two or three-fold increased when you look at tubulovillous or cancer.

Consequently, for example, for calcium, we see an 18 to 20 percent benefit for all adenomas, and 40 or 50 percent benefit for tubulovillous or cancer. And evidence like that provides a very good context to understand how calcium is affecting the whole process of carcinogenesis.

But it would be very impractical and a large mistake to say that only large polyps could be useful as end points in chemoprevention trials of this sort.

CHAIRMAN WOLFE: Can I try to translate your answer if you don't mind? And if I am wrong,

please tell me. To translate what you are saying, you are saying that every polyp is an important polyp in a trial like this.

That you are saying that your answer for number one, for the first part of question number one, is complete suppression isn't the only answer. Other parameters are important, and that means we have to take the polyps out and examine them microscopically.

DR. BARON: I think that is right. Just as in blood pressure, you don't say the blood pressure medication is a failure if it doesn't reduce everybody to a blood pressure of 110 over 60.

And in this circumstance, if you reduce the number of adenomas in a meaningful way, and particularly if you can reduce the advanced histologic features, then with that proviso I would agree with your clarification.

CHAIRMAN WOLFE: Scott.

DR. LIPPMAN: And I don't want to be redundant, but since we are not voting, I just want to say that I agree with that completely. I think until we know more about the biology of these adenomas, for the reasons that you have raised, I would count them all.

But I would based on current level of

science include pre-specified secondary analyses that include what we would consider more aggressive by histology and so on.

And clearly if we had the unexpected finding, and I don't know if any of this that has been shown in chemoprevention, but the hypothetical that somehow you are accelerating the more advanced ones, you would be able to detect that.

So although it is a hypothetical concern, I know of no data at all in chemoprevention that that has been shown.

CHAIRMAN WOLFE: But you still agree that it needs to be -- that this is a hypothetical that we need to look at?

DR. LIPPMAN: Oh, absolutely. I think we should look at it in these studies, but as John said, I would use all of them as the primary end points, and do the biology, and have pre-specified secondary analysis based on what we know, like histology, which we think is associated with more aggressive disease.

CHAIRMAN WOLFE: Dr. Camilleri.

DR. CAMILLERI: I am still struggling with trying to decide what is the most appropriate primary end point though. Dr. Kramer has asked us to consider the complete disappearance of polyps, and perhaps the

proportion of patients who have complete disappearance of polyps would be a more meaningful end point in the context of prevention, rather than in a therapeutic mode.

If we consider today's agenda pertains to chemoprevention, I wonder whether the discussion should at least consider the point that you raised, Dr. Kramer, because to my mind, for instance, a 20 percent difference in the proportion of people who are completely cleared or don't develop anything after an initial and complete clearance of the colon, that would be a very significant difference in my opinion.

CHAIRMAN WOLFE: Dr. Geller.

DR. GELLER: I think that is a wonderful end point, but I think it may be a premature one. I think we are at a point now where from what I have heard today that we take these individuals, and we clean them out, and we put them on -- we randomize them to a chemoprevention agent, versus control, and possibly placebo.

We treat for a certain period of time, and we may do intermediate colonoscopies to make sure that we did a good job the first time. And then at the end of the day, which will be from what I hear here 3 or 4 years after initiation of therapy, we look again.

And what we find is the end point. Now, it could be that the proportion is totally disease free, and it could be something to do with the quantity of disease rather than the number of polyps, or it could be if you wish a number of polyps over a certain size.

But I think I heard that that is not going to yield too many end points. So I wonder at this point if the size of the tumor, the total tumor bulk, the total bulk of adenomas, is measured somehow and seems to be the right end point, with other end points as secondary end points, with plans for the future once we know some more about histology, genetics, or whatever. And possible end points for the future.

CHAIRMAN WOLFE: Dr. Kramer.

DR. KRAMER: And so per your instructions, I am trying to think from the standpoint of FDA; that is, what would get something on to the market for some indication.

So in that vain, I am ont sure exactly how to judge the maturity of an end point, because in order to judge the maturity of the end point, you really have to know what the natural history of that end point is.

And do we know the natural history better

of having zero polyps or the natural history of having a proportion less polyps, and I don't know. I can easily envision that if you were confident that you would have zero polyps, a lot more people with zero polyps, it would immediately translate into medical action. That is, you would not have to do as many endoscopies.

But I am not sure that you could make the same decision if every person had 20 percent fewer polyps on subsequent follow-up. So I don't know how to judge, quote, the maturity of that as an end point.

CHAIRMAN WOLFE: Dr. Lippman.

DR. LIPPMAN: Well, Barry, I think natural history would be very important and help us think whether possibly this is preventing cancer. But still the point is that if these lesions -- and I am not calling them a disease, as Mike and I worked that out at lunch, and I won't use the disease word -- that these things are being treated.

And if they ar larger there is a higher complication rate. So again I think that everything that we are talking about here is on the causal pathway to cancer. I don't think you have to know the exact natural history to do it if you think then treating this particular abnormality.

And if it is smaller, then there is less complications is of value, and in terms of the issue of prevention, one of the things that has really haunted chemoprevention and cancer, and different than in heart disease, for instances, is this idea that prevention has to be a hundred percent complete forever.

And it is not the case for heart disease prevention. We use that same term, and so again we will decide what we think a cut-off is, 25 or 30 percent, and that is meaningful, but I don't think we should all of a sudden redefine prevention in the context of chemoprevention different than what we do for every other disease.

DR. BARON: I would just like to tell Barry that in fact both calcium and aspirin do increase in an proportional manner the number of patients that have no polyps by 20 to 25 percent, and will decrease the proportion with any advanced histology by 40 or 50 percent.

CHAIRMAN WOLFE: Let's try to cut this a little bit if we can, as we are getting a little bit repetitious. But we are all agreeing that in this type of trial, a chemoprevention trial, that every polyp that would be seen subsequent to starting the

trial would be taken out. Does everybody agree with that?

So then we are also saying that since that is taken out that the complete suppression is not necessarily the goal, but it is the ideal idea, but not necessarily the goal. So we would also look at the histology of it. Is that a consensus of this question?

Okay. All other guidelines afterwards will be decided from the results of the trial. Is that what we discussed, and is that our consensus?

DR. GELLER: In particular I don't want to specify the end point of the trials. I think the end point that Barry is proposing is perfectly find if somebody wants to take that on, but I think also a lesser -- one of lesser clinical significance for now could well be acceptable.

CHAIRMAN WOLFE: Okay. Dr. Avigan and Dr. Raczkowski, does that give you guidance for question number one?

DR. AVIGAN: I would just as an addendum ask what the committee and the panelists think about rates of recurrence of polyps on an individual, rather than on a lesion, basis, because we have seen protocols where what is being scored are individuals

who have polyps, versus individuals who do not have polyps at the follow-up exam.

Does the committee feel that this kind of end point is as stringent as the one that they have just described?

CHAIRMAN WOLFE: You will have the answer inherently by seeing the polyps that are present. If they don't have polyps, they don't have polyps. If they have polyps, they do, and we will take them out. No?

DR. FURBERG: I think it is a very important question. I think the unit of anality should be the patient. We are not just looking at lesions. If you look in the cardiovascular field and the coronary arteries, and you remove one plaque and leave four in there, one good have you done?

You really have to consider the patient as a unit.

DR. BARON: This is John Baron, and this is sort of a false issue, because all the studies to date have been analyzed both ways. You analyze the proportion of patients free of neoplasia, and in plus on type models you analyze the multiplicity.

And it is very easy to do both, but you have to do both. Once you do one, you don't

necessarily have the other.

DR. LIPPMAN: And I think they usually correlate.

DR. KRAMER: But again I am trying to think like I am in the FDA, although I am not qualified to be in the FDA, but that is a key question, because yes you look at both, but once you come to the point of saying it is on the market or its not, you approve -- unless both give you statistically significant end points, the question is which one do you go with, and that is another way of saying how do you power the trial, and how many people do you need in the trial.

Okay. Let me propose this then. I would like to propose that the primary end point should be the patient free of polyps, and the second end point should be a reduction in the number of polyps, and also inherently we will assume -- well, we can't assume, because that's why we are studying it -- an improvement in the biology of the polyp.

So that is our primary goal, the reduction and a complete suppression of polyps. Is that the desired primary end point?

DR. CRYER: Mr. Chairman, this is Bryon Cryer. I would just question whether your suggested

primary goal is a feasible primary goal, because if you look at the data that currently exists on the effects of chemoprevention agents, very few of them achieve that goal.

I mean, most of them are just looking at partial regression, and polyps, and so I don't know that we would ever be able to feasibly accomplish a study in which we have looked for complete regression.

DR. LIEBERMAN: I agree with that. I think that if we accept that the polyp bearing population has a greater risk of developing cancer than the non-polyp bearing population, then it seems to me that a reduction in the burden, which could be quantitatively in numbers or qualitatively in histology, is a desirable end point.

And I think holding it to the highest standard of complete elimination, I agree that is probably not going to be feasible.

DR. BARON: As I understand what complete elimination means, it is a complete elimination in some patients. So what I think the chair was referring to was a positive study would be a study in which the proportion of patients with no polyps at the end of the study is increased, and that is definitely a feasible end point, because it has been achieved.

But I think what you may be referring to is a hundred percent efficacy; that is, in every single patient, and that is a different issue.

CHAIRMAN WOLFE: I was referring to exactly -- and thank you for the clarification, and we have clarified each other now.

DR. LIPPMAN: But I do believe that they are both viable end points, but I would reverse what is primary and what is secondary, because different than heart disease -- you know, this is a multi-focus process.

I mean, when you treat someone's cholesterol, that represents the whole body and the risk, but each individual area and polyp is its own independent risk of cancer and being treated independently.

So I think your point is a very valid one, and should be a major pre-specified secondary endpoint, but I would use polyp burden as the primary end point.

MS. COHEN: I want to make sure that I understand what you are saying, that you should not attempt to cure every polyp that you see if they are endenomatous, or anything else, but you should take 80 percent or 90 percent?

That's very cynical. I should think that you would want to do the best you can, and you are not going to be totally effective, but the highest level is what you should hope to achieve. And if you don't, that's too bad, but you have tried. But that is very cynical for the patient.

CHAIRMAN WOLFE: Dr. Geller.

DR. GELLER: I am suggesting that wise minds may disagree on this issue of primary end point. I think we have two and I think they are both acceptable, and I think let the trial designer choose which is primary and which is secondary.

CHAIRMAN WOLFE: FDA, do you want us to make a recommendation which should be primary and which should be secondary or are you happy with just saying they are primary and secondary, and you choose the order?

DR. RACZKOWSKI: No, I think we have heard enough on this particular issue. It does sound like that there is some diversity of opinion. Thank you.

CHAIRMAN WOLFE: We will move on to Question Number 6. In randomized placebo controlled clinical trials of CPAs uses an adjunct to colonoscopic screening or surveillance, what would represent a clinically meaningful effect, size, for

(a) reduction of benign adenomas,

(b) reduction of pre-malignant lesions; (c) reduction of colorectal cancer; (d) increase in the time interval between colonoscopies; and (e) reduction of complications associated.

I would like to start with Dr. Levin to answer this question.

DR. LEVIN: Mr. Chairman, I am going to start with 6(a), and I would like to use two sources for the response. The first is the document that is referred to in the general Clinical Cancer Research by the IEN Learned Committee.

And it states that a 30 percent reduction in the number of adenomatous polyps found in patients treated with an intervention agent, compared with placebo three years after an initial polypectomy, would be considered evidence of clinical effectiveness. It goes on further to discuss the size and statistical probability of such a trial.

The study with which I am most familiar with, and which I am lead co-PI on, it is possible within a large scale trial of fifteen hundred patients to design a study aimed at looking at 35 percent reduction or greater, within a 94 percent power, using a 3 to 2 randomization.

So I would answer that question by saying that we should be looking for something in that range, 35 percent or greater reduction in adenomas, the number of adenomas.

DR. CRYER: I would ask -- I noticed that recommendation as well, and both you and Dr. Gordon previously made that, and on each presentation I wondered how the 30 percent number was arrived at.

And what is so magical about 30 percent to allow it to be clinically relevant is kind of the greater question that I have. I mean, it is a reasonable goal with regard to statistical evaluations, but I am not quite sure of how it relates to -- of how it impacts the clinical relevance of the issue.

Well, the design of trials as you well know, and as we all recognize, depends on a number of factors. It depends on the effectiveness of the agent, and the number of people at risk who might be interested in being involved in such trials.

And the time span of the study so that it is feasible, and that it can be run in a way that would allow one to test the value of an intervention. The particular end point being sortful has to be reasonable enough to be achievable, and not

excessively high so that it can never -- that the goal can never be reached or never mounted.

This kind of level of effectiveness is the one that a number of individuals feel can be achieved within a reasonable period of time, and speaks to the potential for the background mis-rate of colonoscopy being around somewhere between 10 and 20 percent.

And this would enable one to detect an added benefit over that of about 35 percent.

CHAIRMAN WOLFE: Bernie, could I ask you to please just answer -- you gave the rationale, and I want you to do that, but answer all five questions, and then Dr. Cryer is going to answer them, and the rest of the committee.

DR. LEVIN: Thank you. As far as the second issue, the reduction of pre-malignant lesions, I do have a strong bias on this question, because I believe that at this stage of our knowledge it is impossible to tell the lesions that are not on a neoplastic or on a bad neoplastic pathway.

I don't think there are any good adenomas, and so at this point I would have to give the same answer for that question as I did in (a). If it were possible to do a study looking just at advanced adenomas, that answer might be different.

But as we have known from several studies, including the VA study which Dr. Lieberman presented, the incidence of advanced adenomas is sufficiently uncommon as to make any kind of clinical trial, which is what we are talking about today, unlikely to ever been accomplished.

Reduction of colorectal cancer is again a hypothetical question, because there is no evidence yet to bring to that. I would guess that any reduction of colorectal cancer would be worthwhile because of its profound impact on the people in whom it would be found or not found.

As far as increasing the time interval between colonoscopies, possibly a 50 percent increase in time interval would be meaningful, both from a cost point of view and from reduction of complications.

Dr. Lieberman presented data from the VA study on the complications associated with polypectomy, estimating those to be between 0.3 percent, in terms of severe gastrointestinal and other complications, and perhaps ranging up to 0.5 percent.

That is in a very expert group of investigators largely speaking. This is a VA study, and people there have done hundreds or thousands of these procedures, and I would hazard a guess that in

the real world, although the data is clearly not available yet, although the core database may give us some of that.

That the complication rate is significantly higher and that would include unsuspected cardiovascular deaths that might be associated with colonoscopy.

So I think that again something like between 25 and 50 percent reduction of complications would be a very worthwhile goal.

CHAIRMAN WOLFE: I am just going to repeat the numbers that you gave, Bernie. For (a), you gave 30 to 35 percent, and the same thing for (b); and for (c), quote, any number; (d) an increase by 50 percent in the time interval; and a reduction in complications by 25 to 50 percent. Is that correct?

DR. LEVIN: Correct.

CHAIRMAN WOLFE: Dr. Cryer.

DR. CRYER: With regard to (a), it seems to me that what is generating the 30 percent argument is an argument based upon feasibility of a conduct of a study, rather than any strength of that number's relevance to other clinical outcomes, such as colorectal cancer reduction.

I say that's fine, because otherwise we

would never -- and although obviously there is disadvantages to that approach, we would never get these studies conducted if we were not -- if we did not select a feasible end point, such as the 30 percent goal.

Also in the way that I have kind of reviewed the data, it seems to be reasonable based upon the mis-rate of colonoscopy. So as Dr. Lieberman reviewed for us, if you assume that 20 to 25 percent of colonoscopies will miss or 20 to 25 percent of polyps missed on colonoscopy, then an intervention which reduces 30 to 35 percent of polyps would seem reasonable in that comparison.

I also look at this issue qualitatively, in that it seems to me from what I have heard that all polyps don't carry the same risk, and Dr. Lieberman also outlined for us that the small polyps without advanced testalogical features seemingly have or carry the same risk for colorectal cancer as the general population.

So what is more important to me than the absolute quantitative reduction really would be the qualitative reduction in those polyps that have advanced histologic features.

So those would be my responses, and I

would agree basically in the 30 to 35 percent reduction for (a) and (b), with the caveat that it would seem to me to be desirable to have a greater emphasis on qualitative histologic features, rather than all polyps, which may not carry the same cancer risks.

With regard to (c) and reduction of colorectal cancer, Dr. Levin gave us a 50 percent reduction as a potential goal, and I would say -- oh, you said any, and I would agree.

Any reduction, with the caveat that that reduction be in excess of any other morbidity that would be attributable to the chemopreventive agent. So, for example, if a chemopreventive agent had an excess morbidity of cardiovascular deaths, you would like to have that be in excess of the -- you would like to have that be less than the cancer reduction.

And for the time interval, I don't think we have the data, and for reduction in complications associated with polypectomies, any reduction in complications I think would be desirable.

CHAIRMAN WOLFE: So Dr. Cryer pretty much agrees with Dr. Levin, except that you are not willing to put a number on the change in time intervals. You would like to note that there would be some, I

suppose, from the study if we could get that information, but it is not necessary for the initial study you are saying?

DR. CRYER: Right.

CHAIRMAN WOLFE: Okay. And again as far as the benefit risk ratio, that is going to be discussed subsequently, and I also wanted to bring up one point. That although it is paramount to all of us, let's -- and please keep this in mind what our charge is, and I think it is a very important point to leave cost out of it.

Leave cost out, and that we are saving costs by decreasing the number, that will be inherent to the study, but that is not our charge. So again the numbers that we have on the table so far are about a 30 to 35 percent risk, a decreased risk in the development of benign adenomas, particularly the lesions, and any risk in cancer is okay.

And (d) and (e) are a little bit open to question. And again one last thing. I want to again point out that these studies are not going to be-all and end-all. They will be a prelude to working with the NCI for Phase IV studies to determine all these questions with a better degree of certainty.

DR. LEVIN: Can I clarify one thing,

please? I am not sure that you meant this, but I did not want to imply that I had said it. I do not believe that these criteria need to be satisfied by the first trial.

I think these trials inherently are sequential, and they are built on prior knowledge. So I still believe that the first primary data needs to be the reduction in the number of adenomas.

And as Scott Lippman said earlier, subsequently we can begin if we have data that leads us in that direction, and only if we have data that is positive, can one begin to look at some of these other potential benefits, such as extending the interval between colonoscopies.

CHAIRMAN WOLFE: Dr. Lippman and Dr. Richter.

DR. LIPPMAN: Bryon, just to clarify, because any time you try to come up with what you think is a reasonable effect to be clinically beneficial is I think a little bit subjective.

I mean, it is always an issue that if you really pin someone down that it is hard to define. But I was interested just internally in the consistency. In terms of the reduction of these -- or the decrease in the number of these pre-malignant

lesions, you want 30 to 35 percent. But yet you said any reduction in complications would be important.

And if these premalignant lesions that are being removed are directly related to complications, I think maybe that might help us feel more comfortable about a clinical benefit.

You might feel more comfortable about a 30 percent clinical benefit, assuming that is somehow related to complications.

DR. RICHTER: Well, I would actually like to see another end point, because I think without that end point, you cannot answer (d) and (e).

And that is the reduction of patients who absolutely have no lesions, because only if you have on lesions can you talk about extending colonoscopy intervals, or can you talk about cutting down on the number of complications from colonoscopy.

As the studies are designed now, They have a baseline, and probably won't have a one year any longer because we can't get somebody, a third-party payer, to pay for it.

And then you are going to have a colonoscopy at 3 or 4 years, and you are not going to be able to address any of the things about complications or number of colonoscopies, unless one

of the end points is the absolute number of patients that have a totally clean colon at that second colonoscopy.

CHAIRMAN WOLFE: That's correct, but look at the question. The question actually again is what would represent what you would consider a significant benefit for these parameters. Barry.

DR. KRAMER: Although the question is here, that is, the reduction of colorectal cancer, the way that I am interpreting the flow of the discussion is that it is really a meaningless question.

Because if you say -- we have to watch out, because if you say any decrease in colorectal cancer, that means that one extra colorectal cancer death in the control arm, which also means if it went the other way, one extra death wouldn't be okay.

So it is not really a meaningful question at this point. We just don't -- you know, if the consensus is that is not one of the end points that we look at, fine. But to me to really notice any difference, you would need an infinite sample size. And one death in each direction isn't meaningful.

CHAIRMAN WOLFE: Bernie, do you mean a statistically significant decrease; is that what you meant?

DR. LEVIN: Yes, that's what I meant, was any death outside of the confidence intervals. So if it was statistically significant, then I think that one increase or decrease would be important.

DR. KRAMER: That's fine, but I think that is not a practical question here, because we are not even coming close to those end points at this point. If by some miracle it happened, you would have a real winner, but I doubt it would be a legitimate end point.

CHAIRMAN WOLFE: Then, Barry, what would it be then if we had that? Let's say that we had a decrease and we did a trial, and the trial we decided was to look for a decrease in the number of polyps, and we detected a decreased number of cancers, what would you consider significant if it just happened to show in the trial?

DR. LEVIN: In the very unlikely circumstance that a miracle happened, then I would look for statistical significance, of course.

CHAIRMAN WOLFE: Nancy.

DR. METZ: I wanted to ask one question about what do you mean by meaningful effect size? We all I think have taken that question to represent the number of polyps. Can you talk about an effect size

in terms of reduction in size of polyps?

So let's say your control group develops polyps that are on average are 3 millimeters in size at four years, but your therapeutic group develops polyps that are on average seven millimeters in size at four years, would you consider that meaningful?

And I would suggest yes, but I don't know if you actually meant that with that question.

DR. AVIGAN: Well, I think just sort of integrating what was said before about biology, and the fact that histopathy and other biological markers at the end of the trial will be taken into account, we could certainly weave in also size, but with the caveat that once patients are on a drug, the size along may not speak to what the lesions are under the microscope.

But we would be open-minded about all these kinds of characteristics.

CHAIRMAN WOLFE: Dr. Geller, did you want to comment?

DR. GELLER: Yes. I just wonder that if in the duration of the trials that we are discussing, given that we clean out patients initially, I would think that we are extremely unlikely to find a reduction of colorectal cancer.

In fact, we may be unlikely to find any colorectal cancers. So I am not sure if at the stage that we are at now that this is an end-point. I mean, I want to say that I don't think I want to make demands on it.

CHAIRMAN WOLFE: Again, I will be bold. That we are going to recommend to you that we can answer (a) for you, and anything else is a bonus. How does that sound?

DR. GELLER: Well done.

CHAIRMAN WOLFE: So we are recommending a decrease in a 30 to 35 percent reduction. Oh, I'm sorry, I spoke too soon.

DR. BARON: I would like Bernard to clarify if he could your clarification of your original statement, where you said that you didn't mean the 30 percent for the original trial.

Did you mean that as a single agent alone shouldn't be held to a 30 percent standard, or could you restate your amendment to your original statement?

DR. LEVIN: You are restating my clarification of your amendment of my clarification. So, I'm sorry that I wasn't clear. I meant that you should be able to demonstrate a 30 to 35 percent decrease in the number of benign adenomas at year

three.

DR. BARON: Okay. So the celebrex study that you did in FAP wouldn't qualify, although this is a different disease.

DR. LEVIN: Different disease and different circumstances entirely.

DR. BARON: Now, could you advise me of what you would recommend regarding an agent that I have worked with, which is calcium? There was a 20 percent reduction in overall numbers of adenomas, and a 25 percent reduction in the number of adenomas, and a 40 to 50 percent reduction in tubulovillous or villous adenomas, or cancer?

Would you recommend that that not be approved were that to come before the FDA?

DR. LEVIN: If I were qualified to serve on the FDA, I would take that seriously. I think that it approximates the 30 to 35 percent, and particularly because it seems to have an effect on the adenomas, which we believe to have possibly more biological importance. But yet then it doesn't meet your 30 percent --

DR. LEVIN: It comes close, but I would need to look at it.

CHAIRMAN WOLFE: No cigar. Dr. Lippman.

DR. LIPPMAN: I think this is why it is a little dangerous to pick percentages. I tend to be more conservative and would go more negative, and would go lower. But I think it directly relates to the toxicity of the drug. Quite frankly, if I were reviewing the calcium data, given the safety profile and everything that we know, I would vote to approve it.

If the drug had more toxicity, and the drug caused hearing loss, I would want a hundred percent. So I think it does very much depend on the activity, but something as safe as calcium, with data as strong as that, I personally would have approved it.

CHAIRMAN WOLFE: Can we say -- we are all pretty much in the same range, and there are not big differences here, but how about we say a 25 to 30 percent range, taking into account the risk benefit ratio? Does that sound like a pretty good answer?

And everything else -- as for (a) and everything else is a parameter that should be investigated, and if there is anything there, it is a bonus. Otherwise, (a) is what we really aim to achieve in an initial trial?

DR. FOGEL: What about the effect of

histology, which I think was just alluded to? If you see a 40 percent reduction in tubulovillous adenomas, even though the overall effect may be only 10 or 15 percent, would that merit the drug being approved by the FDA.

CHAIRMAN WOLFE: As opposed -- well, your question is let's say there is absolutely no reductions in the number, but the secondary end point is achieved?

DR. FOGEL: The more serious histologic conditions, their incidence is reduced.

DR. CRYER: I think that was the point that I made earlier, and I think that that is actually a very important point. Even if you only get 5 to 10 percent reduction in the small non-histologically advanced polyps, which we are told have very little increased risk of cancer, what is much more important is this much greater 40 percent risk in the histologically advanced lesions.

CHAIRMAN WOLFE: I think everybody agrees that what was brought up though was that divergence is highly unlikely. If we were to investigate it, it is a highly unlikely divergence, is that correct, over on this side?

So it probably would still be considered a

secondary end point, and a very important secondary end point, but nevertheless secondary. Dr. Ransohoff.

DR. RANSOHOFF: I think we should give the FDA a lot of wiggle room here, and not get hung up too much on a number one issue, and it has to do with whether a drug is really safe, and then we can be satisfied with a smaller risk reduction.

The other issue is if it is for a group of people that has a high absolute risk, a small relative risk reduction can translate into a large absolute risk reduction. So I think we should given them room.

DR. LIEBERMAN: I would like to take a slightly different view, and I think this is an important point. Let's say there was a drug that produced absolutely no reduction in adenoma number or size.

But produced a qualitative benefit by significantly reducing the number of polyps that had those changes or high grade dysplasia, and I think that would be an extraordinarily important finding.

And it would imply a completely different mechanism of action than we have been hypothesizing, but I think that would be in my mind probably more important in some respects than the reduction of small adenomas.

CHAIRMAN WOLFE: Let's come back to Anil, and let me ask you this question. Don't you think we should demonstrate that first in a pre-clinical study, that there is such a drug that decreased the biological behavior and biological aggressiveness of the tumor without affecting the size or the growth of it?

DR. RUSTGI: Well, I would echo what you said earlier, that it would be unlikely to have this divergence of affecting histology without affecting number and/or size.

CHAIRMAN WOLFE: You want a pre-clinical study to look at that?

DR. RUSTGI: I would agree that inevitably that all of these agents are going to be studied pre-clinically, but it would be important to incorporate these end points secondary in nature in a human setting as well.

CHAIRMAN WOLFE: Dr. Lippman first.

DR. LIPPMAN: Well, at least in my experience, and I would direct my comment to that, that if that really happened, it would be very tricky, because you are really stuck with your primary end point, and you just would like your secondary end points to be consistent.

So you would be more concerned if you did meet your end point, in terms of overall adenomas, but you accelerated the more aggressive, larger ones.

You know, the fact that you had a drug that only worked on the larger ones, or the more aggressive histology on the other ones, would be again a first for chemoprevention.

I mean, it would be extremely unlikely, but if you had some reason to believe it, you could pre-plan that. But I don't know of Rick has any comments that if the secondary end point was so unusual like this whether -- because then you are always dealing with the possibility that it could be a chance finding if it wasn't powered for that end point.

DR. PAZDUR: Well, statistically we generally don't look at secondary end points until the primary end point has been achieved.

So one would have to -- this would be somewhat of a review issue to be honest with you, but statistically, generally this trial has to meet its primary end point before we even start looking at secondary end points.

Here again it really would depend on the review issue, but one thing that I want to make clear

here, that a 30 percent or some percentage reduction yoo-hoo -- Chairman, yoo-hoo, that at a certain percentage reduction, you are saying in polyp number would constitute enough evidence for approval of a drug for chemoprevention, and this was the point that you were trying to make here.

CHAIRMAN WOLFE: Yes.

DR. AVIGAN: Just since Dr. Richter mentioned the point that patients who do not have polyps is another important -- at the follow-up colonoscopy, is another important end point.

Certainly from a practical perspective, and we are talking about effect size, and what does the committee feel about what would be as reasonable effect size for at follow-up colonoscopy for patients who are free of polyps?

CHAIRMAN WOLFE: Do you want to take a stab at that, Dr. Goldstein?

DR. GOLDSTEIN: Just a quick question. I am not sure that I heard Dr. Rustgi correctly about these drugs do not have a preclinical investigation.

CHAIRMAN WOLFE: No. We were both saying that if we are going to look at the unlikely event that a drug is affecting the biological behavior and causing a less aggressive histology, and less

aggressive biological behavior, without affecting its growth characteristics, that would have to be shown in a pre-clinical study that there is no drug like that so far.

And so even before you would pick that type of --

DR. GOLDSTEIN: Thank you.

MS. COHEN: I have heard calcium mentioned, and I have heard statins mentioned, and I have heard aspirins mentioned. It seems to me that included in this study, whether it is through normal control or something, that you have a chance to look at your graph as to what the CPAs do, and what these other things do, because I am curious to know about the effects of this.

And it might be a lot less expensive for consumers to have that kind of treatment. So I think that has to be included. And may I ask another question? Are we also supposed to be talking about risks involved in all of this? I have not heard it mentioned yet, in terms of other issues, and I would like to talk about adverse events when it is appropriate.

CHAIRMAN WOLFE: We will be coming to risks and we did mention risk, taking into account the percent increase over basal that we are talking about

for an increase for improvement.

The risk benefit analysis must be included in that overall analysis. Dr. Avigan raised a question, and I think we have pretty much answered the question regarding that (a) is the most important aspect of this question, and we have to show reduction of benign adenomas, and everything else would be sort of a bonus.

But he would like to know what kind of bonus would you like to see for (d). What would you consider an increase? If we could increase the interval, because again, although we are not talking about cost here --

DR. AVIGAN: No, what I asked was the percent reduction in the number of polyp free patients at follow-up.

CHAIRMAN WOLFE: The total number of patients?

DR. AVIGAN: When a patient is the unit rather than the lesion.

DR. BARON: I thought that is what we were talking about.

DR. AVIGAN: Were we talking about polyp numbers, scoring average polyp numbers, or were we talking about patient numbers? I think we need to be

clear on that.

CHAIRMAN WOLFE: I thought we had decided polyp numbers is what we had decided.

DR. FURBERG: No, I think there was a split view on that. Clearly, we should use the patient as the unit of analyses.

DR. HOUN: Okay. Let's say -- we heard the percent reduction for polyps as the unit of analyses. What about for patients, polyp-free patients?

CHAIRMAN WOLFE: How about polyp-free patients? Do we have a number for that? That is not one of the questions here, but --

DR. GELLER: Well, let's make sure that we have the first one straightened out. I understood this to mean that you can count the number of polyps in each patient, and that is the outcome, and you can have a 25 to 30 percent reduction in that, and that is one way to do it.

Another way to do it is to consider somehow total tumor burden to be the outcome, and to somehow add up the sizes or -- no? No?

CHAIRMAN WOLFE: I want to bring up that not all of us are colonoscopists. But the average patient doesn't have 25 or 30 polyps. We are talking

about most patients having 1 or 2, or 3 polyps.

DR. GELLER: We are talking about percent reduction on average over the populations.

CHAIRMAN WOLFE: Again, the question that we answered initially was the number of polyps. So the total number of polyps decreased in the study by 25 ot 30 percent. We all came up with that number.

Now the question the FDA would like us to answer are how many polyp-free patients would you like to see; is that correct? Is that the question that you would like us to answer for you?

So, Bernie, do you want to take a stab at that question and Dr. LaMont after that.

DR. LEVIN: I would like to ask for clarification. Are you talking about the number of people who entered the study because they were eligible, and who had an adenoma, or 1 or 2, or 3; and then at 3 years were found to have no adenomas.

And you would like to know whether we want to propose a secondary end point number for that group to use as a means of deciding whether something is effective or not? I am not sure that I understand entirely your question.

DR. HOUN: I think in the first question discussed that there was some split, in terms of view,

on should the unit of analysis be patient versus total numbers of polyps reduced.

And so in recognizing that there is a disparity there, if we just discuss the first half, in terms of 30 percent reductions and total numbers of polyp lesions; and now the second half is discussing what is the percent reduction for if we are looking at the unit of analysis being the patient who are polyp-free at 3 year follow-up.

DR. GELLER: I would just like another clarification. When you talk about these percents, you can talk about the percent relative to base line. So you had three at base line and none at follow-up. You had three at base line, and you had five at follow-up.

Or you could talk about the percent at follow-up, or you can talk about the difference in percents. So I would like to know what we are talking about here, please.

CHAIRMAN WOLFE: If I could clarify this. Your question number one, we answered that; the percent reduction in polyps. You want to now know the percent of decrease in total number of polyp-free patients; is that correct? Is that what you would like to know now?

DR. HOUN: In question number one, there were differences of view, in terms of what is a clinically meaningful --

CHAIRMAN WOLFE: Well, 1(a) for this question, and number of the reduction of polyps. Now for (b), and there is no (b). So this is a question of how many polyp-free patients would you like to see?

DR. HOUN: For percent?

CHAIRMAN WOLFE: No, polyp-free is what you are saying; is that correct?

DR. RACZKOWSKI: I think what we are interested in seeing is the -- and hearing from the committee is what difference in the proportion of patients at some time point would be free of polyps between the two treatment groups.

In other words, some people you could consider to be complete responders at 3 years or whatever, and other people would not be complete responders. And so what difference in percentage of complete responders would you want to see in a drug group, versus a placebo group?

CHAIRMAN WOLFE: Dr. LaMont, do you want to take a stab at that?

DR. LAMONT: I was going to say that there is data in our handout here from the National Polyp

Study, and I imagine that David Lieberman probably has more right on the tips of his fingers and others around the table here.

But most patients have one or two polyps, and so this is not FAP or something like that, where you are looking at the difference between, say, 22 polyps untreated per square something, and 18.

So if the average number of polyps per patient is 1.5, then the number of polyp-free patients and the number of polyps are going to be pretty close together. They are going to be parallel, I think.

There is only a few patients that are going to have more than three polyps. So I think a robust end point would be polyp-free patients.

CHAIRMAN WOLFE: Dr. Baron and then Dr. Kramer.

DR. BARON: I wondered if I could just introduce a little math. Bear with me here. What I think we discussed with 6(a) was the ratio of the numbers of polyps in the treated group to the numbers of polyps in the placebo group.

So that is a relatively reduction in some broad sense of the average number of polyps. That is how I guess we are going to interpret what we already discussed, the 25 to 30 percent.

Now there is another issue. We are looking at the proportion of people who are polyp free at the year three or end point exam, and taking into account Dr. Geller's question, are we talking about the difference between proportion one and proportion two, or are we talking about the ratio of proportion one over proportion two, if these effects are usually expressed as a percent reduction?

For example, a 20 percent reduction. That doesn't mean that 60 percent of patients had recurrence in the placebo group, and 40 percent had recurrence in the treated group.

What a 20 percent reduction is more likely to mean is 30 percent in one group and 25 in the other group. So that is a 20 percent relative reduction.

DR. GELLER: Just a real basic point here. That cancer people usually think in differences, differences in percent, and the heart people think of what you are describing. So we had better be real careful about what we are talking about here.

DR. BARON: Right. That's right. Now, the adenoma trials as they have been analyzed have -- the adenoma chemoprevention trials have usually used a relative measure of association in sporadic colorectal carcinogenesis.

And this end point is usually the primary end point. The multiplicity has in the past usually been a secondary end point. That doesn't have to stay that way, but that is the way it has been in the past.

CHAIRMAN WOLFE: Dr. Kramer.

DR. KRAMER: So actually I think that Dr. Avigan's question was an extremely pertinent one, and it is an explicit recognition of the division of opinion that I have heard here.

Because it is my opinion that absence of polyps, as opposed to relative reduction of the number of polyps, is a more robust end point.

And therefore in part, because of that, I would use that as an end point, and I would allow it to be somewhat less stringent. So if you pick 30 percent, which I wouldn't, as I would go with what Scott Lippman said.

I would pick even a bigger relative reduction, but having said that, I would pick something less for the difference of no polyp recurrence. And let's say if one were to say 35 percent, then I might say 25 percent, or something like that, but it would be less than since it is a more stringent end point, and I would be willing to accept a little bit less.

CHAIRMAN WOLFE: You said 25 and 35. Very good. Thank you, Barry.

DR. AVIGAN: I would suggest that given the time frame work for a chemoprevention trial, and let's say 3 years, it may not be possible or feasible to measure the outcome of polyp-free patients, and therefore would strongly advocate not attaching a number to that end point. Let it declare itself in the analysis.

CHAIRMAN WOLFE: David, and then Joel.

DR. RANSOHOFF: I want to suggest, too, that we want to get away from picking numbers, because we don't need to. It is going to depend on things like is the drug toxic and so forth, and I think it is much more important for this group to talk about some of the things that we have been talking about, but avoid numbers, and things like is it a polyp-free person, and is it a large adenoma, or is it a cancer, or whatever.

And then the details and numbers get sorted out according to the specifics of the study. I think we need to keep in mind that every outcome that we are talking about, while it may make common sense to us, we are all arguing from physiology, and we could be way off.

I don't know what is mandated in the law about using surrogates. I was trying to find -- well, not the law, but regulations. But we don't really have -- we have got common sense here, but there is an awful lot of real hard descriptive data that we are missing to pick any of these outcomes other than cancer, and maybe large adenomas.

I still think that we have to do it, but that is the goal and it is not numbers.

CHAIRMAN WOLFE: Joel.

DR. RICHTER: I would strongly argue that we have got to get back to this hard end point of patients that are free of polyps, because two thing that we don't want to talk about is, one, that whatever these medications are, they are going to cost money.

Number 2, there is going to be a safety issue, and that is going to build up the expense of this. Right now one of the biggest arguments against screening colonoscopies is the cost.

So now you are going to indict a drug or a class of drugs that have some safety issues and you are not going to be able to show that you are going to eradicate polyps in a group of patients, because it is only the group of patients that you eradicate all of

the polyps that you are going to be able to extend their colonoscopy.

And unless you extend the colonoscopy length in a subset of these patients, you are not going to be saving the health care system any money. That's for sure.

CHAIRMAN WOLFE: Once again, even though we all think it is very important, we are not talking about money here yet. Now, I am going to try to summarize, and so we can move on possibly.

When it comes to looking at the specific question, and are we providing guidance for the FDA for designing trials with companies.

And we are saying that the primary end point will be a reduction in the number of benign adenomas. That will be a primary end point, and we don't have to pick an exact number. We can pick a range.

So let's just say 25 to 35 percent reduction, somewhere in that ball park, and taking into account the potential toxicity of the drug.

A secondary goal would be a reduction in the number of -- I'm sorry, an increase in the number of polyp free individuals, which would have a lower number required to be considered significant, and say

in the neighborhood of 20 to 25 percent.

DR. RACZKOWSKI: Dr. Wolfe, just with respect to -- well, I think we did hear a diversity of opinion about what would be primary and what would be secondary.

And I think we have heard enough in terms of the discussion. So I don't think that it is necessary to rank those in terms of what would be a primary and what would be a secondary end point.

CHAIRMAN WOLFE: What I am looking for primarily is what is the range that you are looking for for the reduction. That is the question; what is the meaningful effect size.

So I wanted to get that, and as we are looking for a less stringent number for the whole patient; is that correct? Does everybody agree with that? No? Someone doesn't?

DR. KRAMER: Maybe we are parsing words, but it is not a matter of what would always be the primary end point and then what would be the secondary end point. I think there is a recognition of division of opinion, and some would choose a different primary end point, and that being the case, what would be the threshold for each of the two if they were the primary end points.

CHAIRMAN WOLFE: I stand corrected, because if you use the example that I am most familiar with, and say you can pick PUBs or PAVs, and take your choice, and one can be primary and one can be secondary, but they are both meaningful end points.

So we are talking about which is the more stringent. Do we all agree that the more stringent statistically should be the number of polyps, with a little more leniency towards the number of polyp-free patients?

DR. KRAMER: I am not sure that I understand what you said, but I understood what was said on the other side of the table, and I agreed with it. What they said was that there is a spectrum of opinion about what is the most reliable primary end point.

Having said that, there is a tolerance around as a whole group of each primary end point, and if there is such a recognition that some people will pick one primary end point, and others will pick another primary end point, you have asked what the cut-off would be, and you got a general answer.

CHAIRMAN WOLFE: Okay. As long as you are satisfied, and unless someone here is totally unsatisfied, we will move on.

Question Number 3. I will read it again, and the discussion will be started by Dr. Lippman, but the question is given that mortality and evasive CRC incidence rates are gold standards for demonstrating clinical benefits, what is the relative importance of other study end points of clinical trials of CPAs, such as:

(a) lengthening the interval between, or replacement of, colonoscopic screening or surveillance;

(b) reduction in the number of procedural complications;

(c) other clinically meaningful outcomes.

DR. LEVIN: So I think that (a) -- and again I was going to ask Bryon this, but I am assuming that the reason that he did not take this on at all is because I still feel that this is not something that we will be able to deal with now.

I mean, this is another series of studies once we show activity. So it is not as relevant to these first cohorted studies.

DR. CRYER: That's correct.

DR. LEVIN: Is that correct?

DR. CRYER: Yes.

DR. LEVIN: And I would never suggest

replacement of colonoscopy surrounded by a bunch of gastroenterologists.

CHAIRMAN WOLFE: Not as long as we have any sedating agents with us.

DR. LEVIN: I haven't had mine. And then in terms of reductions and procedural complications. Again, this is sort of redundant in a sense with 6(e), I think.

I think this is an important end point, and again I think that since we know that complications are related to having a polyp that you need to remove, particularly if it is large, I think there will probably be a correlation between polyp reduction, and particularly large ones, and complications.

And then (c), do I think that other clinically meaningful outcomes are important. My answer is yes. I am not sure what they are, but the answer is yes. Again, I think you have to take into account the risk benefit and all these other issues, and I am not sure what specifically we are talking about.

Presumably, anything that you would expect to happen would be integrated as a pre-specified kind of secondary analysis.

CHAIRMAN WOLFE: But you do think that although if we could show a decrease or an increase in the interval, that would be important?

DR. LEVIN: No, I think that is where we would like to go, and I think ultimately that the next series of studies would be testing that question. You know, an active agent, plus a longer interval, compared to the standard interval.

I just don't think -- well, I think that is a long way away.

CHAIRMAN WOLFE: Dr. Goldstein.

DR. GOLDSTEIN: Well, I think all things are relative, and so let me start there. The relative importance, I think the lengthening of the interval is as important as reducing the number of procedural complications.

But I think that both of those lead me to a consideration of something that needs to be included in this, and that is quality of life studies. What you are really talking about here is the quality of life for people with this disorder.

I am talking about mental health, and I am talking about physical health as well. And I will leave in deference to the Chair costs out. That individually these may not reach the gold standards

individually; that is, lengthening or reduction.

But nonetheless taken collectively, they can produce substantial reductions in morbidity, and a much better quality of life achieving both of those. So I think they are both equally important, and to some extent all that we may have at present.

Particularly when you consider number two, which is the reduction in the number of procedural complications. The fact that when we take the lengthening and the reduction in number of procedural complications together, and as has been said here, 25 percent of polyps are missed, I think both of these are of relative importance.

So my answer to Number 3(a) is yes, and my answer to 3(b) is also yes. And there will be I expect improvement in technology, and in materials, and in a variety of other things.

And although I am not a gastroenterologist, I would agree with Dr. Lippman, particularly in a society of gastroenterologists, that I don't see in our lifetimes the replacement of colonoscopy as a realistic goal, or as a realistic occurrence, or likely occurrence.

Finally, I think the other clinically meaningful outcomes, and not directly so perhaps, but

markers of proliferation, and apoptosis leading to better diagnostic and follow-up technology, if I may use that term, are important and in the end clinical.

The industry has and continues to take a very, very serious interest in quality of life issues, as well as of course in individual and diseases. But I would not for a moment -- well, let me put it affirmatively.

I think any time you can lengthen the interval, or any time you can reduce the number of complications, I think you have got to go for it. And I think that quality of life must be measured in this.

CHAIRMAN WOLFE: So you are both saying that these are relatively important. And you are also pointing to the fact that increasing the interval will decrease the complication rate, and I have a question.

I agree with you, but I have a question for Dr. Lieberman to go along those lines. By decreasing the size of the polyps, will we decrease the complication from polypectomy?

DR. LIEBERMAN: I am not sure. I think it is likely that that would be the case if we believe -- first of fall, most of the complications, the endoscopic complications are associated with polypectomy, and the vast majority are probably with

larger polyps.

So I think that is true. I am not sure that we have great data that would actually provide the evidence for that statement though.

CHAIRMAN WOLFE: Okay. Dr. Metz and then Dr. Lippman.

DR. METZ: I am not so sure about that, and my concern is that small polyps taken off with hot biopsy forceps, for example, can cause big time bad bleeding. And if it small and you think you can get your forceps around it, you might be more inclined to use a hot biopsy because it is easier to get it out, and you don't have to use a suction, et cetera, et cetera.

And I think that may expose you to more risk.

DR. LIEBERMAN: And that's why I said I wasn't sure.

DR. LEVIN: But I think one thing maybe we are sure of actually -- and you may another point for me, is that any polyp can be associated obviously. I mean, if you have fewer polyps, small or big, that you need to remove, then you have less chance of a complication.

I would assume that larger ones are more, but obviously we are talking about polyp number, and

you make a strong case for including all polyps, as opposed to just the large ones as end points.

And I just wanted to clarify the issue of other clinically meaningful outcomes. You know, in chemoprevention, at least in other studies that I have been involved with, we are including quality of life, and certainly that was a big issue in the tomoxifen studies modeling and a number of things.

And so I think many of the drugs that you talk about, and certainly it is true with NSAIDs, have other beneficial effects. And I do think that you would want to integrate those into some sort of way as a very important secondary analyses, and these kinds of other clinically important effects.

CHAIRMAN WOLFE: Anil.

DR. AVIGAN: I guess for clarification in my own mind, if others could elaborate, and if the original and historic recommendations about colonoscopy screening are based on expert opinion, and as several people have indicated with a paucity or absence of data, I am not sure if the bar should be set so high linking chemoprevention to influencing the interval for colonoscopy screening and surveillance.

I don't think it has been. Are we saying is it relatively important and we are saying yes, but

it is unlikely to be an end point for the initial studies; is that correct?

DR. LEVIN: I tend to agree with you. I mean, if you take a real hard scientific approach to development of interventions, whether they are drugs or not, you would demand a large randomized control trial.

And that didn't happen with colonoscopies and polypectomies. So whether we go now and say common sense would be that if you have less numbers and are smaller that you can increase the interval, you could probably get a lot of expert opinion that would agree with that.

But coming from a very hard core drug development point of view, I would want randomized control trials. So I understand how colonoscopy and polypectomy didn't go that route, but that is where my comment came from.

DR. KRIST: One thing that I was just going to say here, too, is that number three and the answers to that might follow with our answers to question number six.

And if you have less people who have polyps, or a higher percentage of patients who have no polyps at all, then you are going to adhere more to

screening guidelines, and those patients would get a colonoscopy every 10 years, versus surveillance guidelines, where if someone has an adenoma that you are doing to repeat it in three years.

So that would in effect lengthen the interval, and that would in fact reduce complications, and even though you are not studying, can you lengthen the interval.

You are in effect lengthening the interval, because what you are doing is that you are doing screening, as opposed to surveillance. And I don't think that should be an outcome. But I do think it is something that we can look at as to a potential benefit with the medicines, and it should be analyzed.

CHAIRMAN WOLFE: It is as I termed it a bonus if we find it, and it will involve other studies in the future. So is that pretty much the consensus and are there any other comments on this?

So do we all think that these are relatively important, but no one here would think that these would be primary outcomes, and it is something that should be analyzed, but might take further investigation to determine whether these are truly approachable?

DR. RACZKOWSKI: Okay. Thank you. I do

have a follow-up question with regard to the quality of life. Ordinarily in therapeutic trials, the way that we assess quality of life is by a reduction in symptoms, or improved functioning of patients.

And I wanted some clarity, both from Dr. Goldstein and Dr. Lippman, about in this circumstance where you are dealing with an asymptomatic condition and the existence of polyps, what do you see as being the improvement in quality of life?

Or are you talking about some other adjunctive effects of the drug unrelated to cancer suppression or polyp suppression? Was that clear?

DR. LEVIN: I think that most of it is related to effects of the drug, and the different drugs. So I am sure you have seen that there have been extensive quality of life studies done in the BCPT with tamoxifen.

And this is not my area. We work with people that do this, but even on the big select trial with Vitamin E and selenium, where we don't anticipate a lot of problems, there is a quality of life approach put in there, which measures a little more depth, in terms of how patients perceive it, as opposed to sort of major NCI criteria to the toxicity.

DR. GOLDSTEIN: What I meant in that area

was really lengthing the interval between colonoscopy, and if you will the mental burden in many cases that these people carry, and the burden of people who have had procedures, and don't want to have another one, which is not in the public interest or in their interest.

And a variety of other things related to people who have this disorder. Now, there are some who would question the instruments, and of course they would have to be valid instruments.

But I think it is something worthy of consideration in this, as in so many other fields.

DR. FURBERG: I think it is important to point out that the quality of life is not a one-sided issue. It is two-sided. Quality of life can go up and it can go down.

And what you talked about, Dr. Goldstein, was the positive sides. Drugs have negative effects, and they should also be measured and weighed in with any benefit.

DR. GOLDSTEIN: I agree, Dr. Furberg.

DR. LEVIN: And that is what was done, you know, in the tamoxifen study, which revealed some surprising effects, despite some drug toxicities that are well known, the impact on quality of life negative

was fairly minimal, in terms of normal functioning and things.

And so it really does control for that factor, and it is more relevant with certain drugs than others.

DR. RICHTER: And I am positive about the quality of life issues, but I think you have to understand the limitations of it, because these people do not have symptoms, and they do not have a cancer. So it is not that they have a cancer, and no one is telling them that they have a cancer.

They just have the potential for getting a cancer. I am with Dr. Furberg. I think you are going to find more on the quality of life issue about the side effects of the medications, unless you do your quality of life testing the day after they have their colonoscopy, and then you might have an issue there.

DR. LEVIN: But you are absolutely right. I mean, I think we are saying the same thing. You certainly would not want to win the battle and lose the war.

If you are having a positive effect on polyp number, but the quality of life is deteriorating, you would want to pick that up. And you can't always detect that with classic NCI common

toxicity criteria.

So it really is to control for the fact that if you do see a beneficial effect on your end point, that the quality of life is not adversely affected.

DR. GOLDSTEIN: On the other hand, there are instances in which the quality of life is severely affected by procedural and other considerations, family considerations, in which the drug may turn out to be better, and it is not that common, but it does happen, and I think that has to be considered.

It is merely another way of saying what more do we bring to the party, and how much better can we evaluate, and therefore label, and serve the public.

CHAIRMAN WOLFE: Okay. Dr. Baron.

DR. BARON: I would urge the FDA not to take into account the quality of issues very strongly in prevention, and the reason is that in my experience as a clinician, and as a clinical trial investigator in this area, the prevention area and quality of life is a really loaded subject.

Many subjects feel good and want more colonoscopies, and not fewer, because they feel the reassurance of having that extra surveillance and

there is this paradoxical effect.

This reassurance has been generated by the physicians because of their discussions regarding the National Polyp Study, and the protection provided. But when you look at the National Polyp Study and all the data as Dr. Ransohoff mentioned, the data demonstrating the benefit is simply not there.

And consequently this quality of life benefit that some patients experience with regard to colonoscopy is false. We can create a reassuring feel regarding a chemopreventive agent just by talking it up.

In other words, by advertising, and I don't think that is a very fruitful area for investigation once you get out of symptoms and side effects. I would worry a lot about psychological aspects of quality of life at a very minimum.

CHAIRMAN WOLFE: Is your question answered?

DR. RACZKOWSKI: Yes, thank you.

CHAIRMAN WOLFE: Okay. Are there any more real relevant or burning comments?

DR. GELLER: Briefly, I have not heard the phase of double-blind, and I think if the trial were double-blinded and you gave patients in both arms the

questionnaires at the same time, and away from the colonoscopy, then you would have less of that effect, and (c) reflect the effective of the chemopreventive agent.

DR. BARON: That's true, but if they don't trust the chemopreventive agent, they may prefer to have more colonoscopies because of their sense of reassurance.

MS. ROACH: In terms of quality of life, when you look at it with what you were saying, one of the things that concerns me is that there are a lot of people who would say, oh, one aspirin. No, I will take five aspirin a day. I will take two celebrex instead of one, and five calcium pills.

I think it is getting the message to the public about what the reality is, is a very tricky thing, and I think that anything for approval that you have to be very careful about what you say you are approving it for.

And that concerns me, because this population -- well, you know, it is going to be me in a few years, but it is people who are taking a lot of medicine usually, older people.

We aren't really talking about that topic right now, but that concerns me when we look at this

in the long run, and once drugs like this are approved, if they are.

CHAIRMAN WOLFE: Okay. I think -- well, one more comment. Dr. Lippman.

DR. LIPPMAN: I think the issue that you raised about the double-blind, everyone is getting talked up and getting into these things, and the type of trial that we are talking about wouldn't change the screening and the surveillance colonoscopies.

So those people who want to get colonoscopies will be happy in either arm, and there won't be less of it. And I think with certain drugs and the quality of life, I think that tamoxifen taught us that, and that it can be very, very important.

It is less important with other drugs like calcium and other kinds of agents.

DR. GOLDSTEIN: The very fact that this provoked some heated discussion suggests to me that it is something that at least in passing, or if you play chess, should be considered.

CHAIRMAN WOLFE: I don't think anybody is questioning it shouldn't be considered, but it is clearly -- we are talking about relative importance, and it is not the primary end point. It is something that should be observed, and like in any other study,

you may pick up a benefit, for example.

And let's just say we are using -- and I will just toss this out, a COX inhibitor, and in a group of elderly people, all of a sudden they are thinking clear, and they are not forgetting anymore, and we will just toss that out.

DR. LIPPMAN: No arthritis or any of the other kinds of things, but clearly I was talking about a secondary kind of an end point.

CHAIRMAN WOLFE: We will move on now to question number two. A chemopreventive agent that suppresses polyp growth may in theory cause polyps to become resistant to drug effects.

Additionally, it may preferentially allow small invasive lesions to go undetected on colonoscopy, while large indolent lesions are identified and removed.

If polyp suppression is used as an end point in clinical trials of a CPA, (a) how long should a try be;

(b) what should the time interval be between the colonoscopic evaluations;

(c) what end points and follow-up are needed ot rule out possible resistance to drug effects, differential identification and removal of

large indolent lesions;

(d) how should a rebound withdrawal effect be studied. These are very specific questions which require very specific answers, and we will start with Dr. Sjogren.

DR. SJOGREN: Thank you. How long should a trial be? I think we need to be open-minded about it as you reminded us that today we have a class of drugs, but tomorrow we may have a different class of drugs that have different characteristics and different pre-clinical data, and perhaps phase one data.

So in general terms, I would like to see a trial that accounts for a reasonable amount of weeks, or months, or years of treatment, and say nowadays it is about 3 years of treatment.

And then for a reasonable amount of time of follow-up of those patients, and observing what has been put before us, and I see that the measurements are taken at base line, and then immediately after cessation of treatment.

And so in deciding the trial, I would like to pose to you the question that if this is indeed what we want to advise, or do we want to advise perhaps a longer follow-up after treatment, and a

repeat measurement, and in this case a colonoscopy, 6 months, 12 months, after treatment.

Which goes into the second question, which is what should be the time interval between the colonoscopic evaluations. And that again depends on the agent that we are studying.

But if we were deciding the trial today, I would like to pose to you the question that I mentioned before, which is should we try to prolong the phase of the evaluation and not as the patient takes the last pill, and then the next day do the colonoscopy, because there is still a drug effect on that patient.

And which I think I have seen with question number (d), which is the way perhaps that I would measure a rebound withdrawal effect, and if we come to a consensus on how do we define a rebuttal withdrawal effect.

And I think based on what some of the presenters taught us today, or taught me today, was a number of polyps, the change in the number of polyps from base line in a particular patient.

So if those polyps increase above base line, or compared to placebo, then perhaps if this is the definition that we are going to use, then we need

an interval to measure that.

And I am not sure that doing colonoscopy at base line at year 3, and then at 6 months, and one year after the finish of the treatment is ideal for a patient.

For colonoscopies, the procedure is not that bad, but the preparation is what is rather painful. You know, to be on a strict diet, and to be on laxatives, and to be up all night or all morning, it is not a nice thing for patients.

So if we can minimize the procedures that would be ideal. I think I would like to answer those three questions and then perhaps take a stab at question (c), and then let the Chairman continue on with the discussions in which what end points and follow-up are needed to rule out possible resistance to drug effects and differential identification, and removal of large indolent lesions.

And when I think about this question, I think that there is so many things that we don't know. Indeed, it puzzles me to think that a chemopreventive agent will indeed lead to an apparent lesion that could be quite malignant.

That it will be provoking such a tissue reaction that it just goes against what I know of

medications, but it is certainly possible.

But I think the study of the biochemical and histological study of those lesions will be natural end points for me to evaluate to see if indeed there is a resistance to the chemopreventive agent.

DR. CAMILLERI: Thank you. Mike Camilleri. I think I agree with Dr. Sjogren's comments with regard to Question 2(c) and therefore I will not address that.

I have a perception that what we are talking about here are probably 5 year trials, with the study end points being at the end of the third year of the trial.

But I am going to suggest to you that in order to really appraise rebound that the three months, for instance, that we saw in the data presented this morning to me really are quite ludicrous, and that is really to look at rebound in the context of a biological system that is taking months, if not years, and you probably need to follow up at the 5 year point.

So I want to summarize the way that I think I have heard and that I have learned today the conduct of such a trial. Such a trial would start with an initial colonoscopy, with the aim of cleaning

out old polyps, upon which the Chair and I now agree in the context of a clinical trial.

The second point is that as Dr. Metz mentioned, at the end of the first year there will probably be a second colonoscopy, serving the primary goal of making sure that polyps were not missed at the first colonoscopy.

The clinical trial would therefore be evaluated in a classical randomized placebo controlled period up to the end of the third year, and which would be the study end point.

And then I would like to suggest that the rebound would be assessed at the end of the fifth year. Now, I have a slight disagreement with Dr. Sjogren in terms of how one would define rebound.

And because I am an advocate of the approach of using as primary end point the proportion of patients who are polyp-free as my preferred primary end point, I would define rebound as any patient who develops polyps in the 2 year follow-up between year 3 and year 5.

CHAIRMAN WOLFE: Are you proposing a type of trial in which you have almost a cross-over design?

DR. CAMILLERI: No, I would propose a randomized part of the group design trial, with the

interval colonoscopies at base line, at one year and three year, and then assessment of rebound in the final two years, but the study end point would be at the end of the third year.

DR. GELLER: And treatment would start at the end of the third year? But I just want to point out that in your design, which is perfectly valid, you are making the interval of surveillance two years and not three years.

DR. CAMILLERI: I would defer to Dr. Metz. I thought the study would be a three year study. The end of one year study would be for the purposes of making sure that there wasn't anything missed.

I think Dr. Metz convinced me this morning that a polyp is likely to be found in that first year colonoscopy is likely to have been missed at the base line, and I was convinced by that argument.

CHAIRMAN WOLFE: I a going to play devil's advocate for a second. If you are saying that you stopped the drug at 3 years, wouldn't it be beneficial to take half the patients that are treated and keep them on therapy, and make sure that therapy goes on and is beyond the benefit of 3 years?

And so to see if there is a rebound effect in half the patients, and then go on to 5 years, and

see if there if the duration is more than 3 years?

DR. CAMILLERI: I think one could entertain a trial design which includes re-randomization at the end of three years. But I would defer to others with greater expertise in this area.

CHAIRMAN WOLFE: Okay. Dr. Avigan, and then we will have Dr. Lippman.

DR. AVIGAN: One of the concerns is the word resistance was used, and I guess different terms could be used. But that such an effect and the question of the durability of drug response could occur at any time during treatment.

So that the idea of a short term treatment program or trial rather might not answer the question of whether the desired response to the drug is durable.

So one of the concerns that we have is that we want to make sure that the treatment is along enough to rule out a transient suppressor effect, which then washes away with time. That might be in our argument for your suggestion that a certain arm be maintained for a longer period.

The question that I asked Dr. Camilleri is when he is talking about the rebound, does he mean that patients are actually ceased from taking the drug

after 3 years, and then they have a 2 year window of no treatment?

DR. CAMILLERI: I think the only current clinical design that I can think of is in fact to randomize those who are on treatment to again a placebo versus active treatment arm in the people who have completed three years in the active treatment between year zero and three.

DR. LEVIN: So again I would like to clarify what you mean by rebound. If you treated for 3 years, which I think is a reasonable time. It is not 3 months, and I think 3 years is reasonable.

And if you look at the development of tamoxifen, you start out with one year, and then three years, and then five. And it turns out that five seems to be the magic number.

It is hard to do those second randomizations, although I think that could be considered. But would you consider a rebound if you had a positive effect at three years, and stopped the drug, and then after a period of time the rate, whatever your end point was, was similar between the treatment and the control group.

In other words, the effect wore off, or do you consider rebound where it actually -- what I

consider a rebound where it actually gets worse. The rate increases after you stop. Can you clarify what you mean by rebound?

DR. CAMILLERI: Many of you know that I have no expertise in the biology epithelial neoplasia, and for me to try and give you an answer I think would be inappropriate.

DR. LEVIN: What I was really getting at was not the biology, but at least from my perspective, if you had a drug that worked for 3 years, and then when you stopped it, the rate then approximated; the annual rate then approximated the rate in the control, and that would then be a positive effect for me.

I mean, I wouldn't consider that a rebound. I would consider that the treatment wears off after time, and if you look 5 years later, you will still see a difference.

So again I just want to make sure that we are talking the same sort of thing. You know, drugs wearing off, versus a true adverse rebound thing.

DR. RICHTER: I mean, this might be a naive question, but is there evidence for -- is this a real phenomenon, this rebound that everybody is referring to?

That after you stop a drop, and in this

case in a chemoprevention thing, that as it loses its effect that the recrudescence of that premalignant lesion is more rapid than it was before?

DR. LIPPMAN: That is a good question. In general, what we see is -- we don't see that. We see the rates are approximate. We saw that in head and neck. We see it approximated.

But a true rebound can occur, and the only example that I know of is actually a retinoid study in zuroneuro prematosum, where it was published in the New England Journal of Medicine in the '80s in an NCI dermatology study.

That when you stop the drug that there was a rapid regrowth. Actually, the rate exceeded that, but that is very unusual DNA repair defect. So in general in these kinds of epithelial lesions, the effect wears off.

There is a delay and it wears off, and that to me would not be -- and although I am for a hundred percent forever cure and prevention, that would not be a negative effect. I mean, that would still maintain benefit.

MS. ROACH: I have a question about duration of the study, where it takes 10 to 15 years, is the number that I think I have heard, for a polyp

to grow and turn into something cancerous.

I am not sure how doing something for 3 or 5 years would verify that it is not going to happen in the lifetime of those -- of that part of the colon. I know that I am being fuzzy there in that question, but it just seems that the durations that we are talking about are kind of -- they are shorter than I think might be ideal.

CHAIRMAN WOLFE: Again, I will come back to the original statement. There is no question, and I don't think that anybody in this room would challenge the notion that it would be beneficial, that the ideal study would be -- it is 10 to 15 years in length.

That is not feasible for an FDA type study. That is an NIH study, and again we would hope that if we were able to provide guidance for the performance of these studies that follow-up Phase IV studies would be done, which would be in concert not only with companies, but also the NCI, to look at the long term effects.

On the other hand, some of these studies may pick up certain factors that we are now exposed to, and certain medications and environmental factors that may speed up that 10 to 15 year progression, the

use of certain drugs which may actually cause these tumors to draw faster.

And you pick that kind of effect up by doing randomization and looking at different factors. So at this point I think we are talking about a duration of a study, and we are again going to summarize 3 to 5 year studies. That is what we are looking at.

DR. BARON: I would like to put in a plea that we not specify exactly the intervals. Many of these studies sort of follow on the backs of routine clinical care.

And if there are three year intervals, 3 years and then 5 years is a problem; and 3 years and 6 years is great. So if 5 years is mandated, I see a potential for problems.

The other issue that I would like to bring up is that these drugs are almost never in a narrow sense chemopreventive. They are chemosuppressive, and I think that is what Scott was getting at.

These agents generally attack a process in a way that is effective while they are being taken, and then when the drug is stopped, the process returns to its basal state.

So the idea that an intervention would

cause a permanent prevention I think is sort of naive, and therefore when the FDA devises its requirements, I think it would be very, very important to define exactly what a rebound is, and what durability of benefit is, with or without continued treatment and so on.

CHAIRMAN WOLFE: Well, I think that is the question that is being raised; is there a durability beyond the length of time that the drug is being utilized, but also -- well, I think that is the question that they are raising.

DR. BARON: No, I think when they use durability, they mean with the continued administration of the drug.

CHAIRMAN WOLFE: That would be next, and that is also the same question; is there a, quote, tachyphylaxis, that occurs and in effect stops or you don't see these durability effects. It just wears off.

DR. BARON: I am just putting -- right, I agree with that.

CHAIRMAN WOLFE: And a resistance develops.

DR. BARON: I am putting in a plea for very clear language about a temporary effect that

continues with the drug, versus a chance in the rate after the cessation of the treatment.

CHAIRMAN WOLFE: They are both questions - -

DR. METZ: I would say one way to actually deal with that I think is with Dr. Camilleri's suggestion, which I think is a great design, and requires a number of colonoscopies, unfortunately.

But I think you are going to have to do your baseline colonoscopy enrollment of patients, and a second one to make sure that you didn't miss anything. Your study end point at an interval may be 3 years, at which point you will see if there is an effect.

And then you would have to re-randomize your patients, and wait at least the same or a reasonable period of time and get another colonoscopy to get an idea to answer this whole tolerance rebound, and those sort of questions.

Difficult studies, and big studies, and expensive studies, but probably the right design to get the answers that we are asking.

CHAIRMAN WOLFE: So again just to summarize, you both are saying zero, one, three, and five years?

DR. CAMILLERI: Or zero, one, three, and six.

CHAIRMAN WOLFE: Okay. Dr. Geller.

DR. GELLER: First, I would say zero, one, three, six, and secondly I say put in the consent form that you are going to have a six year follow-up; and thirdly, take everybody off treatment at three years, because otherwise you are virtually doubling the size of the trial.

You just have power to see the effect of this rerandomization, and you are going to need a huge number of patients. It is too complicated and too expensive.

DR. HOUN: Should the trial answer how long a chemopreventive agent should be given to a patient? This was a criticism of FDA on tamoxifen, that the labeling didn't say treat for blank number of years, and studies were stopped. What is you prospective view on that?

DR. LIPPMAN: I can sort of address that, because I agree with Mike's design, whether it is at 5 or 6 years. I mean, I think you want to know what happens afterwards, and the duration of the effect.

And normally, at least with tamoxifen, that would lead to the next study. I mean, if the

effect did persist, then you would be fine. But if it did wear off, and the incidence in the control group, that would lead to the next study looking at a longer interval.

And with tamoxifen, we thought we would go until a full lifetime, and it turned out that it looks like five years is roughly equivalent to 10 anyway. So I think that the recommendation would be based on the design, and I think you need to stick within the study design, in terms of the duration of treatment.

So if it was a three year treatment to your follow-up, that is what I would recommend beyond the label. But in the next study, if the effect wore off, would be to look at 5 years, versus 3, perhaps. So that would be a thought there.

And just to address the other issue that came up about resistance, because it relates to rebound in a way as well. Again, lesions will become resistant. There is no question. There will be -- I mean, these things don't work a hundred percent all of the time.

But if part of the concern is that they would actually accelerate, and they would actually make the biology worse of some of the lesions, and I don't know of any evidence in chemoprevention that

that happens, although we were talking at the break that one would want to look at that.

So in the polyps that are removed on the two arms, you would want to look at histology, size, and maybe some molecular markers to do that. But currently as to my knowledge there is no evidence that it actually accelerates the aggressiveness of the lesions.

CHAIRMAN WOLFE: Can I ask Dr. Lieberman a question? Are you awake? I actually favor 5 years, too, and there is a specific reason, and that's because that number has been used, and can we raise the bar from 3 to 5 years.

And I don't feel strongly on 3 or 6, but I think 5 is what I would pick because that is the bar. Is that it? Is that the one that has been raised recently?

DR. LIEBERMAN: You mean with regard to the follow-up of small adenomas? Yes, I think that is rapidly becoming what is being done in real life practice, and that is deprived from an extension of some of the data that we showed you earlier from the National Polyp Study, which suggests that these patients with small adenomas can be safely followed for a longer duration of time.

CHAIRMAN WOLFE: That is a number that has been bantered about and so it helps to justify that, and helps to investigate that specific question.

DR. LIEBERMAN: Yes, but that being said though, I think the points that Dr. Sandler made earlier are also valid, and that is that we have current recommendations for a 3 year follow-up, and while they are not as evidence-based as we would like, at least based on expert consensus, seemed like reasonable recommendations.

So I don't think it would be necessarily a bad thing to adhere to those guidelines in the design of these trials. Going to 5 years makes these trials much less feasible because of -- and we will talk about dropout later, but that is a significant issue, and the longer that you stretch out the intervals.

CHAIRMAN WOLFE: Dr. Ransohoff, and then Dr. Kramer.

DR. RANSOHOFF: I want to raise a question about the bar and whether 5 years is enough for some groups of people. David, I would disagree with some of what you said this morning, and this may have relevance for how to design trials.

That the recommendation for people with a small adenoma is surveillance colonoscopy every 3 to 5

years. One of the major recommending organizations says -- and this is the AHCPR and the AGA, says that in that group the doctor should have a discussion with the patient about whether any surveillance is needed because of when the acting study, the people with one small adenoma have a normal risk.

And this will have something to do with power, and something to do with whether the group is interesting enough to even try chemoprevention on. And I think if we are getting down to nuts and bolts of trials, high risk groups, length of interval and so forth.

There are some people, even with polyps, who may have risk which is so low that that is going to impact on study design, side effects, and so forth.

DR. KRAMER: As a background, I am hearing several people say there is no science to support what they are about to say, in terms of the interval, and I accept that because I am not aware of any science that would say that one year is better than the next.

So having said that, I am not sure what our goal is here; to design an experiment that each individual here in the room considers the ideal, or to give a range of parameters that are reasonable.

It seems to me that the people sitting

down and designing the study, if they foresee some huge practical barriers to 5 versus 6 years, from what I have heard -- and people are saying there is no real science to it anyway, they ought to be allowed that flexibility.

Others who choose five, that's fine, too. I don't know why we should get caught up on this specific interval.

DR. LEVIN: Mr. Chairman, I would just like to put myself in a patient's shoes for a moment. If I am a participant in this study, such as we have talked about, and I have an entry colonoscopy, and I then go to year one and have another, and have year three and have another.

And then at that point what I am seeking is some clarification of either being in the placebo group, or being in the treatment group, and what happens then, in terms of the design of the study.

I am not entirely sure that I understand what the implications are of this particular recommendation. Can you clarify?

CHAIRMAN WOLFE: No. Michael.

DR. METZ: Well, the way that I was thinking about it, the placebo arm, they can certainly enter into another NCI-funded study, but what I am

really interested in is that the people who have been in the active treatment arm, now I am interested to know what is the duration of the effect, and is there a tachyphylaxis?

And while I accept Dr. Geller's point that it does increase the size of the study, I think the only way to really find out the answer to that point is to rerandomize those patients.

DR. LEVIN: So what will you tell the person who has been in either arm? Will you tell them nothing at year three?

DR. METZ: No, at year three, I would likely offer the patients the opportunity -- hopefully one would have the results of the end of the year three trial, and bring the patients back after three months.

And as suggested by the FDA, you should tell the patients the results of the trial, and then offer them an opportunity either to go on a drug that has been approved by then, and if they have been in the active treatment, and this has been beneficial, and we really don't know how long this lasts, and it is ethically justifiable to re-randomize those individuals, or at least I would find it so.

DR. LEVIN: So your study would have to be

powered enough, and have to have enough people coming in on the front end to have a re-randomization at three year?

And telling people that they have or have not benefited would enable them to make a decision as to whether or not they wish to be re-randomized. And you would have to factor in the fact that if someone perceived that benefit because of whatever, they may choose not to be re-randomized.

I raise some of these issues only to point out that the complexity of such a study, the costs, and the compliance rate, would be very significant factors to the design and success of such a study.

CHAIRMAN WOLFE: We will get to dropout later. Dr. Avigan, you have some clarification?

DR. AVIGAN: I just wanted to speak from again a perspective of perhaps some clinical reality. We have two groups of patients who were being treated; those who were responders after the initial three year window, and those who are non-responders.

And I think it is a very practical question to ask, and again this is a question that we are concerned about. Are there responders continuing to be responders?

Can one assert that Responder A, after

three years, will continue to be a responder after six years, or whatever period afterwards? And not just on a population basis, but on an individual basis.

CHAIRMAN WOLFE: Well, again, getting back to the re-randomization at 3 years, if you do so and the patients have been treated, you will answer the question if there is a rebound effect, and whether the effect is durable, or there is a resistance taking place.

That would give you the answer to both of those questions at that point. The other thing that you may want to do is consider what -- well, think about what do we do with a patient who has been at three years has been on a placebo for three years, and they are polyp free?

DR. GOLDSTEIN: Am I left, or are you left?

DR. LEVIN: All I know is that I am second.

DR. FURBERG: I think typically if a patient who has been in a trial reaches an end point, that is the end of the participation. So if someone at year three has developed a polyp, and has contributed to the study, and reached an end point, you can offer treatment.

I mean, you are primarily interested in knowing those that have not reached an endpoint, and those who are on therapy. It also raises some ethical issues. I don't like the idea at all about re-randomizing or answering a question in the next study. How about if you have positive findings?

How can you rerandomize? Your IRB wouldn't let you do that, and you are unethical if you do it. How can you do a second placebo controlled study if the first one is positive? You only have one shot.

DR. METZ: Can I clarify that if I may? We are re-randomizing people who have not developed a recurrence in the first three studies. So let me just make sure that you didn't understand that I was suggesting an unethical study.

DR. LEVIN: Right, and just to clarify what I think I had said as well. I mean, I think the end point -- the study should be powered designed for the three year end point, and if it is positive, it gets presented to the FDA and you guys on this committee will decide whether it goes into the public health.

I think the secondary end point about durability is a second randomization, and that has

been done before. I mean, we don't need to necessarily need to recreate the wheel.

It was done with tamoxifen, and it was a second randomization, and it was not tremendously powered at that point, and not everyone will go on for people who are disease free.

And you do get useful information, but I just don't -- I would not power the study to do that. I mean, it will give you useful information, in terms of designing potentially another study.

CHAIRMAN WOLFE: One more comment, and then I am going to try and summarize.

DR. GOLDSTEIN: I believe that I was left to right. To use Dr. Avigan's word of reality, and to resonate to Dr. Lieberman, these are complex, costly, and very long studies.

I have some question as to what kind of industry support, except in certain very select circumstances, could be gathered to support them. I think the three year time frame is reasonable, and I think beyond that to commit to resources and everything else to go substantially beyond that would raise some serious questions in the minds of those who manage the research budget.

I am not saying that industry has not done

that, but I think not as often as -- well not very often. Let me put it that way.

CHAIRMAN WOLFE: Okay. A quick comment. We are getting very far behind.

DR. METZ: And just to respond to that. I don't think that is an unacceptable expectation to have though. You will do your study, and you will get your end point, and you will decide if your drug is going to be marketed.

And then you will follow the patients on the drug to see that the end point is a durable one, and I think that is a reasonable expectation that the public can expect, much like with, for example, proton pump inhibitor trials, where your end point for maintenance was at one year, but your safety end point was at three years, and you got your implication after one year. I think that is a reasonable expectation.

DR. GOLDSTEIN: If you are talking about Phase IV studies, then I would agree with you. That is certainly a practice approach, but not very long complex studies before reaching a point where you know it can or cannot reach the market.

CHAIRMAN WOLFE: Okay. I am going to really try and summarize this discussion. This is going to be difficult, because this one has more

diversity I think than any of the points yet.

We are saying that there has to be more than one colonoscopy, and is that fair, more than one? We are saying or it sounded like, and I am going to move back to what Dr. Kramer said in the very beginning, at time zero, one year to make sure that what was indeed clean was clean.

And clean being defined as no polyps seen, and at three years, a third colonoscopy is done to determine the effect of the additional treatment. If the person is found to be polyp free, a re-randomization may be considered at that point for an other period of time, which will be defined at a later time by the FDA, in 2 or 3 years.

And a person who is randomized to active therapy or to another therapy, or placebo, to determine, number one, is the effect durable, and is there a rebound effect from patients who may have been taken off of therapy.

Is that way off or is that pretty much what we discussed? Yes?

DR. GELLER: I really disagree with the re-randomization. I think that the number of patients who will be polyp free is not likely to be a hundred percent of those who were treated or in the control

group.

If you re-randomize both, you are doing a really complicated study. If you just randomize the responders to the chemopreventive agent, you have a very small study that won't be powered to determine anything.

CHAIRMAN WOLFE: We are up to year three. Is everybody up to year three so far, and does everybody agree with that part?

DR. BARON: I think that mandating a year one is a mistake. It creates a patient population that is quite distinct from the usual practice.

It entails expense that may be prohibitive in many cases, and all the discussion that we have had today so far would indicate that the missed polyp issue is one that we are able to live with.

CHAIRMAN WOLFE: I actually don't feel strongly either way. It is not part of normal practice; however, this is a study that we are talking about and so maybe it requires greater stringency. I don't really care either way.

I think that could be left up to the FDA for a year one colonoscopy. We are going right now to year zero, times zero, year three for sure, and everybody agrees with that. One plus minus?

DR. RACZKOWSKI: Thank you, Dr. Wolfe. I think we can go on then with the additional questions.

CHAIRMAN WOLFE: We are going to take a five minute break, a five minute break, and that's it, because we are getting behind and people have to leave.

I would like to regroup here before the break just real quickly.

(Whereupon, at 3:17 p.m, the meeting was recessed and resumed at 3:27 p.m.)

CHAIRMAN WOLFE: Safety is of paramount concern in these trials. So therefore we are going to now move to Question 8, and then Question 9, and we will finish with 4, 5, and 7, and we use the term icing on the cake, and seven is icing on the cake.

So we are going to Question 8 right now, and I will read that real quickly. What is your advice concerning the safety evaluation of a drug proposed as CPA in an at-risk population without active disease.

We will start with Dr. Furberg to answer this question.

DR. FURBERG: Mr. Chairman, I will give my report up. I want to first talk about the factors that we need to consider, and then have three

recommendations.

The first one is that we are dealing with an asymptomatic condition. So for that reason, we need to have a low tolerance for adverse events. And for any decline in health related quality of life.

The second one is that we are dealing with a common condition, and so safety is a high public health relevance.

The third one is that the treatment is life long, and that adverse events are cumulative over the years.

And the fourth one is that there are no surrogates. You can talk about polyps and different types, but there are no surrogates for safety. And so my recommendation would be then to -- the first one is that it is important in the design of the study to have a careful and systematic collection of safety data, relevant safety data.

And indices, various indices, of healthy related quality of life if that is what you want to do. So do that up front and not just pick it up. You need to solicit questions and get the complete valid answers.

The second one is that we need large trials, and I think we are in the right ball park. We

are -- we need for the reasons that I gave, we need to be able to detect uncommon, rare events.

The health benefits of treatment is small in absolute terms, and that's why we need to know about small adverse events also.

The third one is that we need trials of longer duration as you pointed out, Mr. Chair. Ideally, you go on forever, but you have to be feasible, and so I think what we are talking about is trials of 5 to 6 years would make some sense.

If you ask me to give you sort of a ballpark figure about the number of person years per group, I would say between 10 and 20,000. So that would translate to 2-to-4,000 patients per group followed for 5 years.

I think the recommendation made to re-randomize and so on, I think the spirit of that can be captured in post-marketing surveillance. And that could be part of the approval process that the FDA would suggest that the patients in the trial be followed for an extended period.

So, post-marketing surveillance I think is an important aspect of a safety evaluation. And my final comment is that I think I have heard some reference made to feasibility. I don't think

feasibility should drive science.

And we should base science on biology and pharmacology, and that will determine sample size, and that is what I am arguing for. Thank you.

CHAIRMAN WOLFE: Dr. Krist.

DR. KRIST: Yes. To start with, I think that Dr. Avigan did a really good job of laying out the issues of the risks, and just to reiterate one point. I mean, I think that one of the issues with any chemoprevention trial is that the majority of patients are not going to receive a benefit from taking the medication.

So I think one of the key aspects of all of the initial trials to assess whether they are effective is also to make sure that we are assessing their safety. And I think that is a key issue in the trial design, that they have to be set up very well to try and detect adverse events.

And I am concerned about uncommon adverse events, and I am also very concerned about common adverse events, because people are going to be taking these medicines a long time, and there are going to be some at-risk groups, such as older individuals, and people on multi-medications.

So I think there is potential for

significant adverse events. Ideally when thinking about the safety, what I would like to see are that the benefits are greater than the risks.

And I think that one of the tricky things in this situation is that if we are thinking that our primary outcome is a decrease in adenomas, it makes it a little difficult to exactly determine what the benefits are.

If we could say that it decreased colon cancer by this rate, and it decreased morbidity and mortality by this rate, it makes it easier to assess the benefits.

But if we are saying it decreases adenomas, from a cancer standpoint, we can make theoretical assumptions about the effects that it will have for the patient.

And then if you just stick to the direct beneficial effects, like decreased colonoscopy or decreased polypectomy, the benefits are potentially going to be smaller in magnitude, although they are going to be there.

So I think that does make it tricky when figuring out the overall benefit to risk ratio. The other thing that I think about when we are looking at the benefits for patients, which I think is very

important, and just to be able to assess what the studies are, is the benefit to the patient as a whole overall.

And a great example is aspirin and the COX-2 inhibitors, and if you look at patient's risks of having cardiovascular events and dying from a heart attack, it is much higher than the risks of dying from colon cancer.

COX-2 inhibitors could increase the risk of MI and cardiovascular events, and aspirin could decrease it. So the over all benefit between the two medications might be very different.

And I think one of the tricky things which we have discussed here today is that there is probably several phases to this, and the first phase is just looking at the initial implications, and the initial adverse events, and the initial adenoma reduction.

And then the long term phase is to figure out what is the overall benefit, and I am not sure we are going to be able to figure that out initially for FDA approval.

And that is more the important of the long term issues. The final thing that I think about is that thinking about the risks and benefits to patients, patients are individuals, and as

individuals, they are going to have different values.

And one experience that I often run into with this is that I am a family doctor, and I don't do colonoscopy. I do sigmoidoscopy. So I have a big discussion with my patients about colonoscopy versus sigmoidoscopy.

And the thing that you find is that patients put relative different values as to the benefit of detecting all cancers, and even going over all of the data about the potential misses with sigmoidoscopy, a considerable number of patients still are for that.

They place a lower value on the efficacy of higher detection, versus the risk of adverse events with the colonoscopy.

I think for the trial designs what this lets us have to take into account is that I think this is going to be more flexible. I think we are going to have to really assess what the adverse events are, and then it is going to be difficult to assess and rank the adverse events, and what does that mean to individuals.

And that would have to be somewhat open-ended I think, and I will just kind of stop there with those ideas.

CHAIRMAN WOLFE: Let me just say that we actually did discuss this before, and that since we were using the criteria of decreased adenomas criterion, and we all decided that would be the primary end point, or one of the end points, and that there has to be a consideration of the potential for adverse event when we consider the parameter that we are looking at.

So for a drug which has very little in the way of toxicity, we use a lower number, and we would be much less stringent, as opposed to a drug which may have a higher potential for adverse event, where we would use a higher number, and be much more stringent in our requirements. Barry, and then David.

DR. KRAMER: I absolutely a hundred percent agree with what people were saying about the toxicity, and here is how I would translate it into practical implications.

First, it is extremely important to learn what the medical toxicities are, because we don't have a whole lot of surrogates for toxicity, even though we are depending very heavily on surrogates for medical benefits, in terms of the prevention of cancer, and that is what the whole discussion is about.

I personally don't have all that much fair

in post-marketing surveillance to detect safety, and to detect harms. And for that reason, to the extent possible, I would try to incorporate surveillance for toxicities into the trial; i.e., with longer follow-up or longer duration of follow-up.

Just as an example. There is actually an example of a chemopreventive agent, a vitamin, that appears to accelerate the malignancy process, and that is beta carotene for lung cancer in smokers, where it increased the incidence of lung cancer, and the mortality rate from lung cancer, by about 20 percent in smokers who took beta carotene, as opposed to placebo.

Now, I keep asking myself is it conceivable that that would have been picked up in post-marketing surveillance had the trial been at all positive in any aspect, and I think it is inconceivable.

There is no way that you are going to pick up a 20 percent increase in lung cancer mortality absent a control group. And if there is such a problem, and let's say a 20 percent increase in myocardial infarction, or death from myocardial infarction, it will wash away any benefits that we are likely to have detected in the trial, and it will go

undetected I think if it is only a 20 percent increase in a very, very common condition.

So to the extent possible, I would not rely solely on post-marketing surveillance. I would try to build these issues into the trial, and require some follow-up.

And finally, for example, and it has already been brought up, COX-2 inhibitors and its association with myocardial infarction. And clearly if it is true, and I don't know if it really is, but if it is causative, and CO-2 inhibitors increase myocardial infarction five-fold, you have a very tough uphill battle to establish any benefit in preventing colorectal cancer, because myocardial infarction is such a common problem.

And if the infarctions incur well after the trial is over, you may miss it completely. So having said that, I think there ought to be ways to build into the trial itself, and not simply post-marketing surveillance, detection of morbidities and mortality.

CHAIRMAN WOLFE: Dr. Lieberman and then Ms. Cohen.

DR. LIEBERMAN: I would like to post a question to the panel and to the FDA representatives

about this issue. I believe that there are some differences between some of the potential products that we might be considering.

Some have already had extensive clinical experience, and therefore, we have a lot of adverse event information about those kinds of products. Whereas, others would not, and it seems to me the standard for a study, and all the things that Barry was just talking about might be different for those kinds of products.

And my question is really to the FDA people that are here, is to whether they would be able to use data that exists for a product that has already been out there for a number of years, and has a lot of post-marketing adverse event data, even though it is not directly applicable to this particular disease situation.

And the difference then would be for an entirely new product that isn't out there, which would obviously have to be handled differently since we would not know what the adverse events are. So it is really a question.

DR. HOUN: We do have or we do collect systematically post-marketing adverse event data on all the drugs that are approved. The quality of data

as Barry states is variable.

We do believe there is a high failure to report adverse events to the FDA. It is all voluntary. So the best data we have on adverse events comes from the clinical trials companies submit to get approval for indications that are usually short term.

The control data that we have on many indications, even for -- let's say for or of the Category NSAIDs, are short term trials of a few weeks to a few months, in terms of pain reduction or looking at some other end points related to arthritis.

There will be safety data for a year or two years, but again that may be open label uncontrolled data. So the best types of data that we have rarely go I would say beyond six months, because most indications are looking for -- like even blood pressure, we accept 12 week trials for blood pressure medications, and so the best control data is like for 12 weeks.

Although we do get safety data of a year to two years use, but again it is not in a controlled settling.

CHAIRMAN WOLFE: First, Ms. Cohen, and then Dr. Lippman, and then Dr. Richter.

MS. COHEN: Dr. Kramer, you just stabbed

me in the hat. I come from a consumer protection background, and I think that voluntary compliance is an oxymoron.

I think that OTCUs you don't find until afterwards, and you have advertising to the public that isn't always correct. When you have publicity about a particular drug, you sure here a lot of things that people have to say.

Post-marketing surveillance should be longer, and it is effective if it is done properly. And I have to tell you that you surprised me a little coming from NIH particularly.

But in terms of the other -- sorry about that. I won't go into that. I read the presentation that Dr. Avigan did, and I was tremendously impressed with what he did.

And I looked at page 3, and I have that so marked up that you can't imagine, and inverse effects, in terms of toxicity and long use, in terms of in conjunction with other drugs.

I mean, there are so many issues that I haven't -- I mean, among all of you scientists -- and my husband was a scientist -- I have not heard you talk about -- this is one of the most serious aspects of what we are talking about.

And what is going to affect consumers, and what is going to be disclosed to consumers, and so I think that it is extremely important that we know about the toxicity, and what kinds of drugs do I take, and will there be an adverse effect with the drugs that I take.

And how long is prolonged use, and it is all here. I don't need to provide it. Dr. Avigan did it very well here, and I hope to god that it really is done well, and please believe in post-marketing surveillance. I hope that I can convince you.

CHAIRMAN WOLFE: Dr. Lippman.

DR. LIPPMAN: Just a couple of comments. I think that although I would have thought that these are the kinds of agents that you would need to take for life, again I think we need to look at the data that we have, and it doesn't seem to be necessarily the case.

Certainly it does not appear to be the case with tamoxifen, and so I think we may not need to take these things for life, and 3 years may be enough, and 5 years may be enough, which relates to the toxicity issue.

And then the other issue that I think was raised about drugs that are being studied in different

settings, like NSAIDs, and in fact a lot of the drugs that are being developed now for prevention are being developed chemoprevention, and cancer, are being developed for other indications; such as chemotherapy and arthritis, and other issues.

And so I think with a lot of these drugs, they won't be de novo with the first study in prevention. We will have toxicity data from the development of these agents in other settings.

So we will have a better idea of adverse effects in general that can compliment those derived from the clinical trial here.

DR. RICHTER: What I am concerned about in the adverse event profile is too much restriction of the patient criteria as they enter the studies, because when these drugs become available, they are going to be marketed so wide on television that everybody is going to want to take them.

And therefore if there is any type of -- unless there is well-defined adverse effects that say that people with heart disease can't take it, any and everyone -- and we have learned that from several drugs.

And I think it particularly becomes important because we haven't alluded to I think enough

to the nice work that John Baron and the Dartmouth Group has done.

There are natural products that seem to be very effective. Calcium and folate seem to be very effective, and I am not aware that these natural products have these side effects, as compared to these drugs.

So I hope as we look carefully at the adverse events that we will not screw the population such that when we are studying as the healthiest of the heathy, because when the drugs are marketed on television, that's the way they will be sold, is on television.

And everybody is going to be demanding that their physicians give them to them.

CHAIRMAN WOLFE: Dr. Goldstein.

DR. GOLDSTEIN: I think there are a couple of things that need to be said. First of all, the purpose of clinical trials as I have always understood them is to determine efficacy and not safety.

You get some information, but you don't determine efficacy. The second thing is that the true profile of a drug is not really achieved until it has been on the market for several years.

The third thing is that until every -- and

as I used to call it when I was in practice, until every fool -- and I refer to myself with a prescription pad -- had a chance to write it, and every patient had a chance to go in and take antacids with their tetracyclines, or what have you.

The other thing is that there is a whole panoply of methodologies that has grown up in epidemiology and other sciences to allow us not only to do prospective studies, but everything from prospective at the time to the worse of all, the historical controls.

And on many of these drugs, there is a great deal of history that needs to apply. I am not saying, Dr. Kramer, that your point isn't a reasonable one. But I think the true profile of a drug is not reached until after it has been on the market and physicians have had an opportunity to gain some experience with it in the context of the real world.

CHAIRMAN WOLFE: I want to try to answer that, but I don't want you to sound defensive, because you are both right. And Dr. Kramer is not incorrect. The most information that you gain is from the primary study itself, and unless I am way off base, the study itself is not just for efficacy. It is for safety, too.

And post-marketing surveillance is very important, but it is voluntary by nature. Yes, you do get a lot of information, but hopefully the information would be gained in the initial study.

Because if you show the danger of a drug only in post-marketing surveillance, then your initial study failed.

DR. GOLDSTEIN: I am not saying that the pre-marketing -- the pre-approval studies do not gain important information. Of course, they do, but in a controlled environment. And when drugs are released, they are generally released into essentially in most instances a largely uncontrolled environment.

And that is all that I am saying. It has its place, but the primary purpose of studies for approval is to confirm efficacy. The safety is important, of course, but in that period in which you can only study a limited number of patients, whether it is several hundred or several thousand, for a drug that is ultimately exposed to hundreds-of-thousands, or millions, you can see the difference.

CHAIRMAN WOLFE: Dr. Raczkowski.

DR. RACZKOWSKI: Yes. I just want to make a couple of clarifications here. We do evaluate safety in all phases of drug development before

approval, and yes, that data by its nature ends up being better data in terms of safety because it is controlled data.

On the other hand, the points that are being made I think are also valid, and that is that once the drug is released into the market, it is in a much more generalized population.

And so sometimes we do see signals that emerge in the post-marketing situation. However, given that the post-marketing situation is voluntary reporting, often we don't see signals unless they are very, very big safety signals, or very serious safety signals.

CHAIRMAN WOLFE: Dr. Kramer, did you want to say something?

DR. KRAMER: Maybe this has already been said, but we don't -- we should not be setting up a false dichotomy. What I said should not be interpreted as saying if we do it, and if we test for both safety and efficacy in a controlled setting, we should forget about post-marketing surveillance.

The only problem is that if you rely solely on post-marketing surveillance, it has been said better than I have said it about the signal-to-noise ratio changes dramatically, and you can pick up

signals that don't exist, and you can miss signals that are pretty important and serious.

And so given that as a backdrop, and I think by law regulations to do post-marketing surveillance of new drugs that come on anyway, there ought to be a way when you have the opportunity in the trial setting to add on a more meticulous look for -- and less voluntary way of looking for serious toxicities.

CHAIRMAN WOLFE: Dr. Baron and Ms. Roach, and then I am going to summarize.

DR. BARON: Actually, I just had a question for Dr. Furberg. When you mentioned the -- or when you recommended I should say, and I think it was 10,000 to 20,000 person years of experience, was that mainly with an aim towards assessing toxicities, and if so, would you be comfortable with some of these personal years of experience be in trials other than the chemoprevention trial?

DR. FURBERG: It is a ball park figure. It has been work that has been in other settings and I have the experience in the cardiovascular field, and you probably need that number to rule out bad surprises.

And you are right. I would consider it in

other populations also, and add that in. And let me just add for your information that 52 percent of all serious adverse events are not known at the time of drug approval.

DR. BARON: But you were mainly motivated by the toxicity concerns when you recommended those?

DR. FURBERG: Yes, that's correct.

CHAIRMAN WOLFE: Okay. Ms. Roach.

MS. ROACH: I have a comment and a question. In terms of my comment, if this comes out and if the chemopreventive agent -- and we are not talking about calcium or something like that that is already available.

Obviously, we are talking about something like the COX-2 inhibitors, but when it comes out, people will treat it like a vitamin pill. And there are a lot of -- and we all have problems with people overdosing on Vitamin A or Vitamin E because they didn't realize that you could, even though that has been documented for years.

A lot of Americans are functionally illiterate when it comes to understanding the implications of the medicine that they are taking over the counter.

And I think that because of that, this has

to show a huge benefit, in terms of safety, and we can't discount that. I understand the financial constraints, and all of that with the trials, and when these come out, people will eat them like candy is my prediction.

And my question is -- yes, people eat weird candy. My question is that someone said you need to be able to detect rare events, and I think it was Dr. Furberg.

And it is my understanding with colonoscopies that there are colonoscopies that are the normal kind, where you see the polyp. But in order to see flat lesions, you need a special kind of colonoscopy, that includes some kind of dye spray or something.

Is that correct? And if that is correct, is that what we are talking about? What kind of colonoscopy are we talking about, in terms of --

CHAIRMAN WOLFE: We are talking about colonoscopy without using any kind of other agents, or other investigative agents being done to look for dysplasia, but we are not talking about that.

That is investigational, and we are talking about run-of-the-mill, office-performed colonoscopy, without any other agents being used.

MS. ROACH: Wasn't there data in here -- I was trying to find it, and I couldn't find it off the top of my head. But didn't or wasn't there data that showed in animal models that some of the COX-2 increased the rate of dysplasia? No?

CHAIRMAN WOLFE: No, I don't think so.

DR. AVIGAN: I think what you are referring to is that there is an observation that in certain animal models and the animal model in particular was a mouse with a specific gene mutation that was treated with a combination of an anti-inflammatory drug and a EGF receptor inhibitor.

And the polyps were nicely suppressed, but histopathologically there was still evidence of adenomas, and these are precursor lesions under the microscope that were not basically gotten rid of or eradicated.

And that just raises a question of small lesions that are not seen, but that have a potential.

DR. RUSTGI: Well, you may be referring to cromoendoscopy, which allows you to visualize potentially aberrant crypt foci. But that is not really relevant to screening for the average at-risk population.

And there is controversy about the role of

anti-diabetic agents, the glydisones in mouse models, as whether they may be antineoplastic or proneoplastic. And these PPR gamma ligands have received a lot of attention, in terms of potential chemoprevention. But there is controversy in the mouse model literature.

CHAIRMAN WOLFE: We have actually discussed this area before, and that's where we talked about where the polyps must be removed to look at their mitotic index and all other biological parameters.

And that's what we had talked about and how in these studies we will take them out. Actually listening to all of this discussion, this really does not go much further than what Mark said -- what Dr. Avigan said in the very beginning.

That we are going to have to take into account the risk benefit ratio, and that is what we are all saying, and that there has to be a sufficient risk benefit ratio to warrant the approval of a drug.

If the drug -- and again we are not talking about -- and although we all have non-COX-2 inhibitors, there are other drugs here that we are talking about.

Let's say that Drug X causes an extra arm

to grow and prevents polyps at the same rate, FDA will not approve the drug. So this must be taken into account very seriously.

But I don't think we can go beyond that. I don't think that we can pick numbers for the FDA. I think that we are saying, yes, these are important considerations, and you will have to use your judgment when designing a trial. Is that the answer you need to hear?

DR. RACZKOWSKI: Yes, thank you.

CHAIRMAN WOLFE: We will move on to the next question, and that is going to be Question Number 9. For partial or complete suppression of adenomas polyps, (a) should a portion of patients who experience the clinically meaningful benefit of polyp suppression exceed the proportion of patients experiencing serious adverse events? That is a real tough question.

(b) if yes, should the study be powered according with why or why not;

(c) in order to ensure long term safety of CPAs, what should the length of the clinical trials be. And we are going to start with Dr. Geller on this question.

DR. GELLER: I did keep looking for the

trick in the first question. I kept on putting in numbers, and I could never come up with a scenario for a negative answer.

So the benefit of polyp suppression should always exceed the proportion of serious adverse events.

CHAIRMAN WOLFE: Does anybody disagree with that?

DR. GELLER: Okay. Fine. If yes, should the study be powered accordingly, and I think not. I think the study should be powered for efficacy and large enough for that, and not to worry about the adverse events as the primary end point.

And I guess the last question really has been discussed over the course of the day. We sort of decided that the length of trial should be 3 years, but I really like tacking on a longer time for maintaining follow-up.

And I said this earlier, and I think that a colonoscopy at 5 or 6 years is a good idea. And I think if you promise that as part of your trial to the patient, you can continue to before approval. So I guess if the drug is not approved -- and the thing is that once you stop, it is hard to get going again.

So that is a big of a problem. I think,

yes, I guess I would keep the follow-up because you will never know what you will find in that follow-up. I mean, you may find that the benefits are late, for instance.

And that might lead you to new hypotheses and new trials, and you may find that something that you have approved that maybe you shouldn't have. But it will give you better data if you can keep following the patients.

DR. HOUN: So just to clarify. You are suggesting that the trial go for a colonoscopy for like at year six, and then submit the findings for risk benefits?

DR. GELLER: No, no. I think you can submit on the basis of year three data.

CHAIRMAN WOLFE: That's what I was asking.

DR. GELLER: I'm sorry. I didn't understand.

CHAIRMAN WOLFE: Dr. Avigan.

DR. AVIGAN: I don't have anything to add to points A or B. On point C, I would agree under the ideal circumstances that one should engender a situation where one can check long term efficacy or safety of these chemopreventive agents at a colonoscopy at 5 to 6 years.

But I would reiterate what Dr. Baron said. I think there are pragmatic considerations that are mitigating and that it really makes compliance difficult. It makes it extremely expensive, and there are all sorts of hurdles that need to be surmounted then.

DR. GELLER: You won't get as good data as you got in the trial. I have no illusions. But you get better data than you will get by post-marketing surveillance alone.

DR. AVIGAN: I would agree, and so we are faced with this dichotomy of what is ideal and what is pragmatic in a situation like this. I would also ask what the experience has been for a similar approach for chemopreventive agents for other neoplasms, and let's say what has been the requirement for demonstration of long term safety for CPAs in other neoplasms.

CHAIRMAN WOLFE: Real fast and to summarize what both of you said, yes, no, and around three years, with a hope for a follow-up to look at safety.

And I just want to add one thing about (b). I would give a qualified no, because you have something with which you know ahead of time, and to

approve a drug for something else which has a high toxicity.

For example, it causes strokes. You know that it does that, and you want to make sure that you look at that very carefully, because actually Dr. Avigan used that example.

He used the example before in the question about the jury is still out about the COX-2 inhibitors and thrombotic events. You may want to consider the possibility of considering that where it would be a qualified no.

Efficacy is more important in this case than safety would be.

DR. FURBERG: I think there is a contradiction here. Nancy said no to Number (b), that the studies should not be powered to provide adequate information about safety, and then under (c), she said yes.

It should be that the length of the trial should be to ensure long term safety. So there is a contradiction, and I have to say that I agree with the (c) answer that, yes, we need to take safety into account in determining sample size.

CHAIRMAN WOLFE: So you are saying yes, yes, three?

DR. FURBERG: Yes, and I can give you the example. Since '97, the agency has withdrawn seven drugs, and four of them were approved based on surrogates.

So there was a surrogate efficacy with small studies, and later we found out that there were safety problems. So this is an illustration that you shoot yourself in the foot if you are too eager to approve a drug based on small studies' effects on outcomes like frequency of polyps.

You need to take safety into account, and that is for patient safety.

CHAIRMAN WOLFE: So the only controversy we really have at this point is really (b), and that is whether or not the study should be powered to pick up a safety issue; is that correct? So, then let's just discuss (b) for now then.

DR. BARON: Well, I was just going to clarify. I think that Dr. Furberg a minute ago said that if you already know about the toxicity profile of a drug, then there is no problem.

For example, if you were studying aspirin now, well, we know aspirin does cause strokes in people without vascular disease.

DR. FURBERG: I agree. We are talking

about new chemical entities, but for aspirin and calcium, I am perfectly content with what we have.

CHAIRMAN WOLFE: You can't power something that you don't know.

DR. GELLER: Well, one of the problems is that it is hard to power a study for an unknown toxicity. But the other thing is that if you have fairly good follow-up for an additional 3 years, I don't think there is a contradiction. I think you will have more toxicities possibly, and better data.

DR. FURBERG: Well, I gave the ball park figure of 10 to 20,000 person years, and so that would satisfy me.

DR. GELLER: I don't think you are going to get that on the initial trial of a chemopreventive agent in colorectal cancer.

CHAIRMAN WOLFE: Dr. Kramer.

DR. KRAMER: I agree that what Nancy said doesn't on its face seem to be a contradiction. I think that we are choosing by design here, we focus on surrogate end points, and it is important in longer follow-up to see if there are medical downsides to this decision.

And some of the worst surprises of course are toxicities that weren't known at the beginning of

the trial, and for which therefore you can't power up the trial or in particular when they are going to occur.

In answer to the question about what are other chemopreventive agents, and tamoxifen, and to my knowledge that is the only cancer -- well, I should not say prevention agent, but it is an approved agent to decrease the risk of getting breast cancer in high risk women, although that may be fine tuning the word prevention.

But it came out of the NSABB, the National Surgical and Breast and Bowel Program. I don't know whether this is FDA rules, but I do know that in the NSABB that once you go into one of their trials, they follow you for good.

And they have -- and therefore they were the first group that picked up the fact that tamoxifen causes endometrial cancer. And they did it because women that were on their trials in long term follow-up, and not through post-marketing surveillance.

And I even question whether post-marketing surveillance would have ever detected it, because tamoxifen was out there for three decades.

CHAIRMAN WOLFE: David.

DR. METZ: I would suggest and I feel very

strongly that I agree with this prolonged follow-up, and this brings up another potential advantage here.

If we are talking about a surrogate end point, we are arguing about what is the right end point, and we are as good as we can be, but we definitely are not choosing the ideal end point.

We are looking for 3 years because we are trying to be practical about what is the appropriate time to get some kind of end point. And now we are talking about the third issue that is a little controversial, and that is how safe are we going to ultimately be.

Therefore we go back to the original design of having another or at least some of your patients carrying on for another three years. You get a lot of benefits out of that, and you certainly are not going to get definitive answers, but you will learn a lot.

CHAIRMAN WOLFE: Can I ask the FDA a question? If you approve it for three years, is the cat out of the bag, is that it? I mean, it is much harder to withdraw a drug than it is to not approve it in the first place; isn't that correct?

DR. HOUN: I think that the issue with the drugs and how easy it is to withdraw depends on a

couple of factors. One is the indication. If your indication is trivial, and improvements in not a life-threatening condition, or not a life-saving indication, then the tolerance for a life-threatening or serious adverse events may outweigh your benefit.

The other issue is are there other alternatives on the market for your indication. But I do think we are in the position that prior to approval it is better to get the questions answered prior to approval, because safety concerns that develop after approval, if they are life-threatening and fatal, that puts everybody in a poor position.

CHAIRMAN WOLFE: Another question. How often do you see -- let's say in 5 years something that was not even trending in 3 years?

DR. HOUN: Usually in the market, if a drug has a serious adverse event, we will see it within 3-to-5 years. It depends on the dissemination of the drug use. If it is a big uptake drug, then you are going to see it sooner.

If it is a slower dissemination drug, you might see it for a while. I have a question related to safety on the class of drugs NSAIDs. This is widely talked about and studied.

We know NSAIDs have a risk for GI bleeds,

and some of them are serious, and it is very interesting that the GI folks here are the ones that handle that complication of GI bleeds, and yet you also are the ones that handle polyps, and polyp prevention through colonoscopy.

And I want to get an understanding in terms of looking at this class of NSAIDs, and the risk for bleeds can be in one year 2 percent, 4 percent. And then your expectation for polyp reduction after 3 years, people were saying that is 30 percent.

And so I am just wondering in your own mind how you figure out this risk benefit for NSAIDs in general with GI bleed.

CHAIRMAN WOLFE: One thing that I would assume, and I would like to have Dr. Cryer answer this, too, is that I am assuming this question is going to relate to COX-2 selective inhibitors, and I am not going to get into the issues of the vigor and class studies.

But I am going to still believe that these two will ultimately prove to have a lower bleeding rate than the non-selective NSAIDs. So I think we are talking about on the balance sheet that these will be beneficial with regard to reducing polyps, as opposed to causing more bleeds. Bryon.

DR. CRYER: So I think that the whole issue that you have brought up is what has led us to currently evaluating other classes of agents, and specifically COX-2s, for their potential as a benefit as chemopreventive agents.

And specially the problem or the previous problem was that the risk of proximal upper GI events with non-selective NSAIDs, despite the fact that there was reasonably good data that showed that they were chemopreventive, outweighed their efficacy for chemoprevention.

So how I view this really in terms of the risk benefit analysis for COX-2s is that it appears as if their risk reduction for upper G.I. events is going to be half as much as seen with the non-selective NSAIDs.

So you take that 2-to-4 percent that you just suggested, and you cut it in half, in terms of the risk. And then we have to see ultimately what the benefit will be with regard to reduction in the lower-GI tract.

Now, what percentages you use really depends on what the end point is, and in the example that you just gave, you suggested that it would be the polyp -- for the 30 to 35 percent reduction in polyps,

and that would be the comparison.

But the way that I see it, although that is not what we are currently discussing, but when I ultimately do this risk benefit analysis down the road in my mind, it is going to be the risk of upper-GI bleeds, compared to the benefit potentially of cancer reduction.

CHAIRMAN WOLFE: Dr. Lieberman first, and then Dr. Fogel, and then Dr. Levine.

DR. LIEBERMAN: I was going to say that I agree with those comments. That I think with the end points that we have commonly agreed on in this panel, that we have a very special burden regarding safety issues, because the end point is of somewhat uncertain benefit, and in which I think all of us would agree on right now.

And therefore I think we have a special burden not to produce harm. So I think that the recommendations to perform a 3 year study, but then to have an extended follow-up of these patients with safety as the criteria of the follow-up, has got to be probably built into whatever study you end up accepting.

Because there really should be very little tolerance for serious side effects. We don't know for

sure if this benign polyp reduction should we see it is actually going to translate into a colon cancer mortality reduction.

CHAIRMAN WOLFE: Dr. Fogel, and then Dr. Levine, and then we summarize.

DR. FOGEL: I think the question that was asked is a very important one. I think for entry into the study that I don't think that the risk of bleeding should influence how the study is designed.

However, for the interpretation of the results, if there is a significant risk of bleeding, and we don't know what the benefit is in terms of cancer reduction, or what the significance of the polyp reduction figure is, then it may not be something that should be approved.

But I don't think we can answer that question right now.

DR. LEVINE: I am not sure that I agree completely with Dr. Fogel. I think we have the background of aspirin, and clearly we are just learning now, and it took a long time, and our chairman certainly knows it better than anybody.

And Dr. Feldman and others who have studied prostrate gland and E1s and E2s and the tissues, both in tissues in Gis and elsewhere, that

the 81 milligram dose, which is presently going to be used in most of our elderly patients now, has much less risk than the higher dose aspirin for GI bleeding.

It still has risks, but it is much, much lower. My concern is that the dose that is being used in these studies, and whether as pointed out before, once it is on the market it will be much higher doses probably used as pointed out by Nancy.

So I think it is very important for us to look at dose. And my feeling is that you won't know a lot of the results until this study is over, and I think you may be surprised that it is not as safe.

And all of us have seen around this table large ulcers, bleeding ulcers, from COX-2 inhibitors. Maybe half, and that's correct, and maybe 20 percent of the others, but it is a large number and I think that dose is critical.

That we have to look at the dose that the trials are looking at, and look at if dose makes a difference, and I think it will.

CHAIRMAN WOLFE: Okay. So getting back to the question. So, (a) is yes; and (c) is 3 to 5 years; and (b) is I think -- and going back to what I said before, it is no in general, because you cannot

anticipate adverse events, and the power for them.

But if there is a known adverse event, you may have to consider that in the equation. Is that fair? If so, we will move on. We will go to Question Number 4.

Should the results of the clinical trials in individuals at high risk for CRC be generalized to individuals at normal risk for CRC, why or why not. Please specify the criteria that should be used to classify risk in clinical trials of CPAs. We will start with Dr. LaMont.

DR. LAMONT: This is a somewhat confusing question. I didn't get it until after I spoke to a few people about it here.

But it seems to me that if we are talking about sporadic colorectal cancer that we are talking about, and average risk patients, and that is patients without a hereditable or acquired disease. So we are just talking about regular risk patients or normal risk.

Therefore, the question is hard to answer because the patients who are going to enter into the trial are normal risk for CRC if I understand the question properly. Unless we select patients who have already had a polyp, which is what we want to do.

CHAIRMAN WOLFE: That is likely to be, and to start with someone who had a previous distributed polyp and is at high risk.

DR. LAMONT: So in that sense then, it wouldn't be absolutely generalizable. But we want to select patients with polyps, because otherwise we would have to study tens of thousands of patients.

So I think what we really want to discuss is how do we classify risk here, and it seems to me that the factors would be age, and that is a known factor for a polyp risk and cancer risk.

And that we wouldn't study anybody under age 50, and that the types of polyps that we are interested in are those that are over a half-a-millimeter, or excuse me, 5 millimeters or greater.

And that are adenomatous polyps, and we don't want to study any other kind of polyp. They don't matter. And aside from that, I think that those are the two main risk factors.

So entry into the trial would be patients over 50 that already have a polyp it seems to me.

CHAIRMAN WOLFE: There was a plea before, and I just want to address the plea about looking at patients under age 50.

And sometimes we can do this in some

trials, and include a certain percentage of people under that age, because we all do see the occasional patient, and that is the patient that we actually do want to very carefully prophylax.

So you may want to consider it as a group relaxing that age 50. Do we all agree that adenomas and polyps is what we are talking about here? We all agree with that.

And with the age, I think we should discuss a little bit.

DR. LAMONT: Yes. There are small numbers of patients that have polyps below, and I just looked at some data, and it is between 40 and 50, and it is a tiny number.

And maybe we should talk about upper range, too, because a comment was made before about not taking out a polyp in an 80 year old, and I think we have to be very careful about how we structure this.

But in general we want patients who are at a high performance level, because they are going to have to jump through four hoops of colonoscopies and a whole bunch of other stuff. So you would have to be less than 80 at the end of the trial.

DR. GOLDSTEIN: I would like to ask a

question. What about the high risk categories, such as those like my daughter, who has had IBD for more than 30 years?

You arbitrarily cut it off at 50, and it is a question. What would you do for those people?

DR. LAMONT: I think that is a very special population where you first of all would not consider some of the drugs that we have already been talking about as a chemopreventive agent.

And I think it would muddy the water. And I would talk about people that have no genetic or acquired risk, known risk factor for colorectal cancer.

DR. GELLER: I am going to argue against an upper age bound, and rather base the criteria for entry on performance status rather than limiting the age of the patients that you enroll.

I don't think that we should have age discrimination.

CHAIRMAN WOLFE: Again, you are looking at black and white. You have to be very careful, because some drugs have an age related toxicity to them, and you have to look at the age, and look at each individual age.

And so I think that age has to be taken

into account. We are not picking a definite age. Are we talking about a policy that the FDA should consider. We all agree that their minimum age should be considered, and they can decide to consider a minimum age later on.

The question is should an upper age limit be considered, and I would argue that in certain cases it might be considered.

DR. METZ: One point about the lower age. There will be a fair number of patients who are motivated to get a colonoscopy by the age of 50, and who have a clinical indication to have a colonoscopy.

For example, a family member who developed colon cancer below the age of 50, and there will be a number of those patients who would clearly be motivated to get into this trial, and would potentially have a polyp found, and would qualify.

And I would say that those are the very patients you would want to study.

DR. RACZKOWSKI: In just reading the question I am wondering if we are not addressing the intent of it as written. The question as stated is about the application of a trail finding to groups other than the ones that were perhaps studied.

And we seem to be talking about the entry

criteria for an ideal study. And so maybe if the FDA could clarify exactly what they need, then we might be able to focus the discussion.

Well, one of the issues with Phase III efficacy trials is whether or not the patients that are enrolled in that trial are representative of the ultimate population who will get the drug.

And the real intent of the question is to what extent do you think that if patients who are enrolled with high risk criteria into clinical trials, should those results be extrapolated to patients who are at normal risk.

CHAIRMAN WOLFE: Just so everyone understands, it is those or that the trial would likely include those who had previous polyps. Let's say it shows as a benefit, and are we now going to allow the approval to be for everybody in the population?

Look, here is a high risk group, and they benefit and that means that you can benefit, too. Don't even get in that category in the first place. You will never have a polyp this way.

So are we going to allow to extrapolate these studies from a high risk to a, quote, average risk, which means no risk or the same risk?

DR. BARON: Sorry, but for a further clarification, listening to Dr. Avigan earlier, and in trying to read his mind, I think he would say that one or two small polyps would not really be a high risk population.

So again are you referring to a trial done among -- for example, people that have big polyps, ugly looking polyps, or lots of polyps, and generalizing down to the solitary polyp forms?

Or are you talking about solitary polyp people, versus the whole world?

DR. AVIGAN: Right. I think we have to be careful whether we are lumpers or splitters. We are talking about a heterogenous group of people, who varying degrees of increased risk, depending on what their characteristics are.

So they might include people with multiple polyps, or people with single large polyps. There are people who have compelling family histories, and each of them, if you start analyzing them as subsets, can be assigned specifically different risks.

But I am distinctly not talking about people who have single small tubular adenomas that from what we have heard today, and from what seems to be borne out in the literature, do not convey an

increased risk.

CHAIRMAN WOLFE: Then you are going to have to define what a high risk patient is, because the definition used in the past is if you had a previous polyp, an adenomas polyp of any type, you are at risk at developing a second one.

I am going to ask Dr. Lieberman if that is what your feeling is.

DR. LIEBERMAN: The epidemiologic data certainly suggests that people that have had polyps have had an increased risk of developing cancer. So that represents a higher risk group than those that don't.

We have slightly conflicting data. David Ransohoff mentioned the Wendy Atkins study from the early 1990s, suggesting that a patient who only had a distal small adenoma, that they are at risk over 14 years of follow-up for colorectal cancer was not greater than the general population.

So there is a little bit of conflict there, but overall most of us believe that if you had had adenomas, then you have an increased risk.

DR. FOGEL: For the population that does not have a family history, and does not have a history of polyps, it is very difficult to justify the

conclusions of a study in which you are looking at polyp recurrence.

It is not clear that you would have the same efficacy. You do have to worry about the risks of the drug then outweighing the benefits, since we don't know what the risk of polyp development is.

So I would be very reluctant to extrapolate from the studies that we have talked about of polyp prevention to the general population.

CHAIRMAN WOLFE: Dr. Rustgi.

DR. RUSTGI: I think that you really need to stratify risk. I mean, it is a continuum from average risk to moderate risk, and high risk, and by using the term high risk it is causing some confusion.

I would apply high risk to a strong family history and then the known inherited syndromes. That being said, I would agree that I would not extrapolate from findings in high risk population groups, where one has to furnish proof of principle, which is important.

But I would not extrapolate it to the general population or the average risk.

CHAIRMAN WOLFE: I don't think we are talking about here about -- you're right. True high risks, and those with familial syndromes of any type.

We are talking about the moderate risk and those with a previous history.

DR. RUSTGI: And with those people at moderate risk, I would not apply it to the general population or average risk.

CHAIRMAN WOLFE: Let me summarize then, and again we will see if we disagree from here. We will talk about the moderate risk to people with previous polyps, and what type of polyps are left up to the specific study design.

We all agree that we cannot extrapolate to the people with average risk, or no risk, or no previous history, no family history, no nothing. And that the criteria to be used will be adenomas polyps for trials, and that age will be a consideration. Definitely with the bottom end, and possibly with the upper end.

MS. ROACH: I disagree with the upper end on the age, because I think you need to mimic the real world in something like this.

CHAIRMAN WOLFE: I understand that, and again you have to take into consideration that there is certain drugs that may have a very significant toxicity at the upper end, and that has to be taken into account by the FDA.

So we have to leave them some leeway that being the possibility. If there is a drug which causes significant toxicity over age 80, for example, and that does happen, and let's say a non-selective NSAIDs with the risk of toxicity is quite significant.

You have to consider that as a possibility and not consider that in a trial. Yes?

MS. COHEN: I have a question. Suppose someone develops polyps and there is no family history, but they all of a sudden have polyps, are these people not eligible for this clinical trial?

I mean, suppose the typical and average consumer as they use in consumer protection develops polyps, and there is no family history, but they do have polyps. Don't you want to know what the general population where there is no historical pattern --

CHAIRMAN WOLFE: Of course, but you also have a problem of causing significant problems for that patient. Every single drug trial takes that into consideration; that a person has a serious risk for developing a complication and they are not included in the trial.

That is the exclusion criteria for any study, and so the FDA has to have some leeway in that regard. If they know that there is a drug that has

been shown to have significant toxicity in the elderly, which does exist, they have to have the ability to exclude that patient population.

Any patient population who has blonde hair also, and they can exclude that patient population if they determine that. So I think you have to have that leeway to have that possibility.

DR. LIPPMAN: In my original statement, I also used size here, and I think we should probably revisit that with perhaps input from experts on this, and I said 5 millimeters or greater.

Because if in fact smaller polyps don't increase the risk, then we want to front load the study to come up with some meaningful data. We should perhaps define in addition to having had a polyp, what the size of that polyp should be, or possibly even location. But size.

CHAIRMAN WOLFE: That would be a detail to do then and for the FDA to decide what constitutes the risk that they are looking for. Did you want us to decide that for you here?

DR. HOUN: It's okay.

DR. METZ: I just wanted to mention that I think that the point has been made, and I just wanted to reiterate it. I think it would be very wrong to

take data from this study even if it is very nice and very positive, and extrapolate it to the general population who has not been screened before.

My big fear here is that when this is potentially available, people are going to say, oh, don't worry. I don't need a colonoscopy anymore. I am just going to go into Drug X and that is going to be fine.

And I think the data that is going to come out of this kind of trial is that people at risk have a reduced risk, and it has nothing to do with the person who is at average risk and who has never been scoped.

And I think that your average risk scope at age 50 is something that I think we should make sure is maintained.

DR. RANSOHOFF: I think we should be careful about trying to anticipate the future too much and proscribing things that we don't understand a lot right now. The key question is that if studies are done in people of medium risk, and not HNPCC or APC, the median risk, and we want to extrapolate to other groups people with somewhat lower risk, the key biological question is whether the mechanism by which carcinogenesis occurs different in people with lower

risk, compared to the group that you studied.

It is quite likely in the future that we are going to know a lot more about pathways and mechanisms, and might be able to generalize. And I think the only thing we can say with certainty right now would be don't study HNPPC rate and APC and try to generalize others from that.

I think it is plausible, but we don't know or are unlikely to find out that the mechanism of risk is the same in a variety of different groups and will learn that in the future.

CHAIRMAN WOLFE: There are studies actually being conducted right now if I am not mistaken about the NCI looking at people with average risk. But we all agree that we cannot extrapolate at this point. You all agree with that? Okay. Let's move on.

And question Number 5. Should clinical trials of CPAs be required to include substantial numbers of individuals' particular demographic or base line characteristics, such as age, race, or sex, or on a particular concomitant of therapies, such as NSAIDs? We will start with Dr. Fogel.

DR. FOGEL: The study that I think we are talking about is a study in which patients who have

had polyps and had the polyps removed are then entered into a study where they receive the chemopreventive agent.

I think we should be certain to include African-Americans, and possibly in a greater oversampling of them because of their different natural history.

There should not be any gender exclusions and so I guess that means that it is not a VA study.

And I don't believe there should be any age exclusion if the individual already has a polyp. I would not want to include young individuals if they have not had polyps previously for the reasons that we have already talked about.

The second part of the question has to deal with concomitant therapies, such as non-steroidal agents, and I think we should probably include calcium and some of the other chemopreventive agents.

I think given the information flow on the internet and elsewhere that many of the patients will be on other chemopreventive agents, and it is probably going to be necessary to stratify the patient population, because I think if you don't, you are going to end up with a potential confounder of results.

CHAIRMAN WOLFE: Actually, Dr. Levin had to leaven, but this is a more difficult question than it looks, because if you use other agents, you may make the bar so high that it would be impossible to show an effect above, and that brings up some ethical issues about not allowing other medications in there which have been shown to have a benefit.

So the way that I feel, I am not sure I know the answer to this, but it is not quite that simple a question.

DR. GELLER: Once something is shown to be efficacious, you may just give it to everybody, and yes, it raises the bar, but it should.

CHAIRMAN WOLFE: I understand, but you may make it impossible, which is even better yet.

DR. AVIGAN: There is one very practical issue, which is low-dose aspirin, because many geriatric patients are on it for prophylaxis and cardiovascular disease.

And just as a very practical matter, the question is, is the chemopreventive agent redundant? Is it additive in its chemopreventive effect, or is it possible that they cancel each other out, or have some combined effect which is not salutary.

So from that perspective, with that agent,

because of its disseminated use and advocated use in the same population of patients, this is a very practical matter.

DR. FOGEL: In the study design that Dr. Levin talked about earlier this morning, he actually stratified his patients into those that received low-dose aspirin and those who did not. And then half received placebo, and half received the chemopreventive agent.

CHAIRMAN WOLFE: Obviously, also you would lower your percent increase over basal if you know that something had an effect there.

DR. CRYER: That was the exact point that I was doing to make there, but I just wanted to say that it seems to me it is at least fairly clear that we are stuck with having to include low-dose aspirin in any of these trials because of its cardiovascular protective effects.

MS. COHEN: NIH is doing something very interesting. In the Washington Post, they are advertising for people to participate in clinical trials.

I would like to see inner-city people have the opportunity, who don't have any kind of health system available to them, and one of the things that

you can do is go to the churches, and advertise that they are looking for people to enter trials.

And I think it is very important that we have a diverse population. And I have been at this long enough to know, although there are things mandated, that it doesn't always happen.

DR. LIEBERMAN: I wanted to raise a slightly different twist on this issue, and that is just overall general reliability of trials that enroll patients that have agreed to have three colonoscopies in three years.

Arguably, this is a population of patients that may have other health seeking or health modifying behaviors, and it might affect the general reliability of the results.

For example, these people may have made dietary changes, and they may be taking aspirin, and they may be taking calcium because they read Dr. Baron's study. They may be talking foliate. They may be exercising regularly.

They may be consuming low-fat and high fiber. I just wonder whether from your points of view whether this troubles you at all, because these are obviously confounders.

And whether you think that the studies to

at least collect this information. I agree that I don't think we can ask for stratification for all these things, because there is too many.

But should we be collecting this kind of information so we have a sense of whether these populations resemble the general population.

DR. RACZKOWSKI: Just a quick answer. Yes, I think it is pretty standard for most clinical trials to collect information about concomitant medications or herbal products, or other sorts of dietary supplements.

DR. KRAMER: And I would say in a nutshell that you just described something that is known as healthy volunteer effect, and that is built in by the statisticians into their sample size, and assumptions.

At the very best, we are not going to -- we almost never get a population that exactly reflects the target population. But to the extent possible, I think it should be tried.

So that the last thing that we would want after a trial is to have a pretty good answer in people who don't take low-dose aspirin, and then people pour in who are on low-dose aspirin, and they cannot take it and get an answer, and that after 5 years, and $20 million, we don't have a clue.

So whatever the target population is likely to be, that should be incorporated into the target population for the trial.

CHAIRMAN WOLFE: Okay. Should clinical trials be required to include, and the answer is yes, right? The answer is yes to everything? Now, the last question -- didn't Carmac used to say that? No, the last answer.

The last question. How should drop-outs or sensor patients be analyzed? And I think I wanted to start with Dr. Lieberman.

DR. LIEBERMAN: Yes, you did, but I don't know the answer to this one.

CHAIRMAN WOLFE: I wanted you to look bad.

DR. LIEBERMAN: That's right. In general, in clinical trials, you do an intention to treat analyses, and in this case, obviously there could be lots of reasons for drop-out, and if one of those reasons is adverse events, that is going to be an important thing to record and document.

And that somehow is going to have to be analyzed differently, and I am not a statistician, and so I have to admit by ignorance here about how to deal with that. Barry, were you the other commentator on this?

DR. KRAMER: I can't do much better, except that when you are looking for time to event, you do try to incorporate into the Kaplan-Meier analyses the intent to treat philosophy as your primary analysis.

You can always do retrospective subset analyses, but the primary analysis is intent to treat. And then there will be censored patients, and then maybe Nancy can comment on this.

But the assumption for all of these curves that we generate is that the censored patients are people who would have had the identical outcomes as the others. That is, that censored patients are non-informative.

You look for hints that they may actually be informative; that is, there may be different reasons. People may drop out of one arm in a trial, and may drop out because they are having myocardial infarctions.

And people who drop out of the other may just drop out for inconvenience or whatever. You want to be sure that they dropped out for similar reasons, but censored points are always difficult.

You hope that the drop-out rate is no lower than a certain percent, and at least in the

cancer trials, where you often look to see that fewer than 10 percent dropped out, but that is not always perfectly reassuring, and you can comment on these designs.

CHAIRMAN WOLFE: We need your guidance.

DR. GELLER: I am a statistician, and the first thing you should do is try to minimize drop-outs, and this sounds just so perfectly clear, but in fact you should really have in your trial design retention plans, and things to do.

At the Heart Institute, we give out mugs and tee-shirts, and things like that. So something to help a retention is really a good idea in the planning.

The second is that the number of drop-outs, or the time to drop out in each arm is informative. You really want to know if the drop out is unequal in the two treatments.

If in particular you have a treatment with some toxicities, Dr. Kramer said you don't want -- you may see a larger proportion dropping out there. The third thing is that what you are doing to do about the drop-outs should be preplanned for the data analysis, and there are a number of methodologies that can be employed.

One of them that Dr. Kramer suggested is that you assume that the drop-outs are non-informative, and then you would censor them at the time that they dropped out.

We know that is not true, I guess, and so I would like to say that that is not an optimal solution to the problem. A second possibility is the worst case scenario. You think that people dropped out because they failed in one arm, and didn't fail in the other arm. So you can do that.

That is usually too stringent and there are other possibilities. Statisticians are very good at making up data according to prognostic factors, and the methods are called imputation.

And I think that all of these methods are possible, and may well be acceptable. They just should be preplanned, and it is an issue that the designers of the trial should think about while the trial is planned and not when you are stuck at the end of the day.

DR. KRAMER: I agree with that, but the only thing I would add is that we can beat you. We don't give out mugs in our trials. We give out gift certificates and club memberships, and things like that.

DR. GELLER: Well, we can't beat the pharmaceutical industry, Barry.

CHAIRMAN WOLFE: Dr. Goldstein.

DR. GOLDSTEIN: That leads me smoothly into talking about the pharmaceutical industry. Thank you for the sewage. In actual fact, a wide variety of techniques, too numerous to recount here, are used, including inducements and all sorts of recruiting efforts and great care with inclusion and exclusion criteria, and everything you have said and a good deal more.

But as we all know, with reference to the question, FDA pays particular attention to deaths and drop-outs, and the key there is to analyze to an excruciating degree every death and every drop out, and to document it to a fare-thee-well, and that in the normal practice of pharmaceutical medicine is what is done.

DR. GELLER: I actually think that too many drop-outs by itself should be reason for non-approval. I was privy and a party to approval of something that had too many drop-outs.

I knew that it had too many drop-outs, and there was an imputation method used, and the drug was later withdrawn. The drop-out rate was something like

30 percent, and that is just out of the water.

DR. AVIGAN: I just wanted to mention that the drop-out issue is very relevant to colonoscopy trials, and the drop-out rates, for example, in the National Polyp Study, which we cited today, were quite extraordinary.

And there was something in the order of 50 percent, and that was somewhere at that 3 year time line. And that is because of the -- that may be because of the colonoscopy and the fact that people don't like to have colonoscopy, even in a study setting.

And I was going to ask Dr. Lieberman whether from his experience that he thought that studies could do better than that based on motivating patients, and if not, whether such numbers of drop-outs would be very problematic.

DR. LIEBERMAN: I am pretty convinced that we can persuade almost anybody to have a colonoscopy if it is done right. I will tell you that in the VA study of the 4,500 patients that were eligible after all of the exclusion criteria, one-third elected not to have a colonoscopy. So there was a percentage of patients, but two-thirds of the patients ultimately had a complete colonoscopy done.

DR. BARON: I think there are two issues here, and I am wondering if the FDA wants us to clarify this. There are two kinds of drop-outs. Actually, there are two words here, dropping out and censoring.

And one problem is that patients don't get a colonoscopy, and the other problem is, and it is somewhat unrelated, they stop taking the drug; or they start taking the drug on their own if you are doing something like aspirin.

Now, these two issues are conceptually, and unfortunately they have to be handled a little differently. The intention to treat business is quite easy if they stop taking the drug, but they undergo a colonoscopy.

Then it is a no-brainer. People who don't get a colonoscopy for whatever reason, including death, that is another story. So I think it might help the FDA more if we explain our recommendations, in terms of these two separate dimensions of dropping out.

DR. GELLER: I was talking about not getting the end point in what I said earlier, and as for whether or not you take the treatment to which you are assigned, I hope you do. I want you to very badly.

I implore you to do so, but if you don't, I am going to count you in the group to which you were assigned anyway. I believe in intention to treat analysis, and I don't think anything else should be used for drug approval.

CHAIRMAN WOLFE: Okay. So we will leave it to the FDA to discuss with the statisticians regarding the criteria and the number of patients, and basically we are going to use ITT as the method for designing the trial. I think that is the last question. Is there anything else that anybody would like to discuss?

If not, I want to thank everybody, and all the panel, for all the hard work, and all the diligence, and I want to thank the FDA for their input for this meeting. Thank you very much.

DR. RACZKOWSKI: And I wanted to also extend my appreciation for everybody's involvement. We had a very ambitious agenda, and the discussion was very helpful and very illuminating, and for those of you who stayed and didn't drop out, you can pick up your tee-shirts and your mugs in the lobby.

(Whereupon, at 4:46 p.m., the meeting was adjourned.)