

CENTER FOR MIND-BODY MEDICINE
COMPREHENSIVE CANCER CARE 2000

CONCURRENT: Methodological Issues in CAM Research

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MODERATOR: Stephen Sagar, MD

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P R O C E E D I N G S

DR. SAGAR: As you can see, we have some very eminent researchers here today. You can tell that by the number of portable laptop computers they have brought in.

Out of interest, how many here are physicians?

(Show of hands)

DR. SAGAR: How many here are physicians who do research?

(Show of hands)

DR. SAGAR: How many here are PhD researchers?

(Show of hands)

DR. SAGAR: Administrators or government?

(Show of hands)

DR. SAGAR: Anybody else? Oh, what are you? Press, okay. Right, press. That is worth knowing.

The format is that we have 20 minutes per speaker. Following that, we have approximately half an hour of interaction and discussion. During the discussion, if you could come up and use this microphone, because this is being taped.

The three guests we have here have all been pioneers in developing methodology and research. One of the emphases that we wanted to put on here, a big emphasis we want to put in this conference this year, is research.

We have got to the stage now where clearly there is a major public interest. However, clearly some systems and techniques work and others don't. The research, I think, is very challenging in this area. It moves away from the standard paradigm of pharmaceutical type research. On the other hand, the basic tenets of the science do apply.

First, I would like to introduce Carmen Tamayo. Dr. Tamayo works at the NCI Canada for the Center for Behavioral Research and Program Evaluation, and the task force on alternative

therapies with Canadian Breast Cancer Research Initiative. She is also doing research, consulting for University of Texas Center for Alternative Medicine Research and Cancer.

Currently, she is director of the Complementary and Alternative Medicine Division of Foresights Links Corporation, which focuses on research and development. Please welcome Dr. Tamayo.

(Applause)

DR. TAMAYO: Thank you very much for being here. I am grateful to the organizers of this meeting, and of course all of you for attending this presentation.

I just want to start actually reading something that I consider a prayer, but it is actually regarded as the oath of Mimonides. She was a prominent physician. She said something that I would like to read. You can follow, hopefully. "The Eternal Guardian has appointed to me to watch over the life and health of thy creatures. May the love for my art actuate me at all time. May neither avarice no (unintelligible) nor personal glory or for a great reputation engage my mind. For the enemies of truth and philanthropy could easily deceive me and make me forgetful of my lofty aim of doing good to thy children.

"May I never see in my patient anything but a fellow creature in pain. Grant me the strength, time, and opportunity always to correct what I have acquired, always to extend its domain, for knowledge is immense, and the spirit of man can extend indefinitely to enrich itself daily with new requirement.

"Today he can discover his errors of yesterday; and tomorrow, he can obtain a new light on what he thinks himself sure of today. Oh, God, thou has appointed me to watch over the life and death of thy creatures. Here I am, ready for my vocation, and now I turn onto my calling."

I do believe that this is actually the call of all the people who are present in this room. I do believe that we have to learn from past mistakes and that we have to look for better ways to do things.

I do believe that we have to turn to God sometimes to ask what we're doing wrong and how we can improve and I do believe that especially this particular field of complementary and alternative medicine, there is too much that we need to learn.

I want to present you actually a very quick overview and forgive me if I don't explain everything. You will have time for questions after this. But I want to just to emphasize the fact that CAM has been, now Complementary and Alternative Medicine, the domain of CAM has changed over the years. That's funny. The last one that is published actually at the Web page of the National Center for Complementary and Alternative Medicine includes five different domains: alternative medical systems, which are Oriental medicine, Chinese, Ayurvedic medicine, homeopathy, naturopathy, mind-body interventions, which include meditation, art therapy, prayer; biological based treatments, which are basically herbal therapies and special diets and dietary supplements, and manipulative and body-based methods, and energy therapies like Qi Gong, Reiki, among others.

Some characteristics are not unique to each one of these. They vary across and within domains, but I want to emphasize the ones that I believe are common to each one. Basically, they are not currently seen as a part of conventional medicine. That is what I think that we are here today.

We are here today because we somehow want to integrate what works, and we want to be able to offer it to everybody.

Patients play an active and key role in healing. This is in my opinion good and bad. It is good because it gives you the control and the sense that you can do something for yourself. It is good for physicians, actually, because in a way it takes out the responsibility that if I am not doing something fine, it is not my fault. It is actually the patient's fault. But it also actually gives kind of a sense of guiltiness to the patient because if they are not doing well, then it is their fault.

So I guess it is actually interesting that the fact that it is important in the patient is basic -- is the basic part of this. But it actually could be very (unintelligible).

Definitely most of them, not all again, can have individualized treatment plans. I know that a lot of people like the word "paradigm." Definitely there is a kind of paradigm in terms of etiology of disease, etiology of healing, etiology of consulting. There is a multifactual etiology.

Multiple treatment modalities -- I really think that that is shared by many of this, not necessarily one is best than other, it is just that they are multiple, and multiple symptom profile.

Again, it is the patient who actually is the one who has their answer to those questions, and I think that we heard this morning very nicely. If you want to know about something about the patient, ask him.

As a patient, I think that, you know, don't hesitate to ask. I know that this is a very heterogenous group of people here, and I don't want to be oversimplistic. But I really think that, you know, as any human being having information or anything, I think that it is important to ask has the method been objectively evaluated?

Has the method been evaluated or used in a case similar to my case? Is the information reliable? Can I really count on that? Has it shown potential benefit?

I think that those are questions that everybody can ask. Researchers can ask these ones. Patients can ask these ones and health care and policy makers can ask these. And (unintelligible) of the activity, that is actually something that we will discuss. Anyway, trust but verify.

In terms of research, again I will give very quick overview of methodology because I want to give more time for questions. But I think that the NIH group published a nice paper in 1997 about the research. I think that the major conclusion that we are -- major, different conclusions. But I really think that the major ones were researchers should use the strongest design available.

That doesn't mean that, you know, you cannot create one design. It still has to be strong. Clinical trials are not the only game in town. As a matter of fact, I do believe that there are several interesting initiatives going on in this area right now where actually we can get objective evidence not based only on randomized, double blind, controlled clinical trials. These will be actually shown probably later.

Complex complementary medical systems and approaches can be studied as a whole and I want to present you just a short sample. We did in Vancouver an evaluation of integral medical

clinic a prospective outcome system developed again by the NIH group and the Office of Alternative Medicine. And it was interesting.

We followed ten patients, you know, that were using a specific treatment for cancer, alternative, and in-depth practice of the doctors. And we actually analyzing these results. But they can be evaluated as a whole.

Many of the biological treatments, especially herbal and vitamins, may be treated as a conventional drug. With that, I don't want to say that you have to select and develop a new drug. I do believe -- and I think that Mark Blumenthal has been promoting this, and other people at the Botanical Council. Herbs can be a study as a whole as well but they should be studied conventionally.

CAM research methodologies, where we have a qualitative method -- qualitative, I put that one first because I do believe that is the one that is more applicable maybe to what we really want to achieve in complementary medicine.

It emphasized experience of participants. I think that most of you agree that a story, it is worth more than -- it is like a picture is worth more than 1,000 words. I really think that a story is worth more than a 1,000 clinical trials.

Data collection in -- there are varieties in that are unique to each method. But, you know, the data collection is important in qualitative research based on interviews and examination of documents. There are focus groups, case studies, triangulation.

I'm not going to go into any of those details. I just want to make sure that you understand there are a variety of methods that are used, that have been used, and can be used.

Quantitative research, that is the one that everybody, when they think about changing paradigms, so it seems like that -- they say, oh, you know, that is what they want. They want only, you know, quantitative; they want numbers. They want something to measure. But I do believe that we have to rely on those methods as well.

Definitely, the very best example is experimental. It is our RCTs, or randomized controlled clinical trials. They are observational and a quantitative method of research. And like cohorts and case control and studies and service, observational studies can be controlled or not controlled. The observation can be in a single patient or it could be in a group of patients.

Using experimental, of course, a result presenting numbers and then investigate the influence, the way in which interventions are administered. In observation, though, investigators do not influence the course of events.

There are also recent methodologies that are classified by duration of the study. There are prospective studies, where you can actually diagnose something that is the "dx" there. Then you start actually the treatment, and you follow up, and you look for an outcome, and you follow up the patients, and you evaluate the outcome, whatever it might be.

In retrospective studies, actually, as the word says, you know, you look back at how the treatment was administered, when it was administered, and you actually start with the results and see how those people did with a particular treatment or intervention.

The (unintelligible) level of evidence -- there are many. And it has been classified several times. I couldn't find one that I liked a lot, which actually is apparent, where number four is the base, and number one is the peak of the pyramid. Probably (unintelligible) will have that one in his computer.

But actually, that pyramid there, tells you about, you know, what we think that has the strongest objective in it. What provides me the strongest evidence? And one, it is well-done, systematic review of two or more clinical trials. Then we have the randomized, and that's their order. But remember that someone told me, or actually anecdotal evidence, is the base of that. We have to start with something.

I want to go to some methodologies that haven't been applied, to the best of my knowledge in CAM research. And this is actually an initiative that was, you know -- yesterday, there were two sessions devoted only to evaluation of best cases. And that's great. I really believe that that is where we are going. We need specific cases to inform what is going on. We need the practitioners to tell the public and to tell the researchers and to tell the clinics what are we doing.

Yesterday, this doctor from Germany presented his cases and this is a good initiative. This is the way it goes because that is the only way that we can get information to go ahead and apply that as needed. Typically the best case requirements, I'm not going to take again much time on this. The objective essentially is to facilitate for the integration of complementary medicine within our health care system.

You should have and need to have documentation for diagnosis. If you have cancer, that needs to be confirmed by pathology. That can be confirmed by, you know, other methods that can be actually at least be observed.

The severity of illness should be given as well. It is important to determine, naturally, the treatment received, i.e., how you administered the treatment. When did you administer? Did you combine the treatment with something else? I mean, at what point the treatment really -- you know, you really started treatment. And I guess the whole point of this is reproducibility.

And my question yesterday was, okay, this is great. This is happening in Germany. I would love to go to Germany to one of those spas if I had a cancer, to be honest. But, I mean, is that applicable here? I mean, can anybody go to Germany and have a two weeks wonderful treatment and be cured of cancer?

I think that we have to think about reproducibility. We have to think that some of the things that are applicable in other cultures may not be applicable here, or how can we integrate those? Those are the questions that I would like actually you to respond. Of course, adverse events and outcomes. I mean, that is important.

I have heard people saying -- and I have many papers saying, you know, there is never adverse events when you are taking natural treatment or, you know, complementary, alternative treatments.

That goes actually without paradox of the individual. You know, the individual doesn't want to fail anything. So probably they don't report the fact that they are not -- that the treatment is not working.

So it is really important to rely that, you know, we need -- that is why we need the research. We need the research because we can be more objective. That doesn't mean that we're able to take out the value of the information that the patient is providing us. On the contrary.

Anyway, what is clinical effectiveness? I believe that this is just how we can actually measure what really works, how that things work. You have it from the patient, whatever they are, with a specific diagnostic, with a specific interest, with a specific ability to be healed, with a specific control over their disease and over their decisions.

We have an intervention that may be anyone, and we have an outcome. That's actually the bottom line of everything that we are trying to provide.

Randomized controlled clinical trials -- I think that having these other two presenters here, I am not going to get into the details of this. I just want to let you know that, you know, it is actually a clean way to tell us how a treatment works.

However, the undertaking of RCTs does not guarantee valid results, and the finest RCT of the same intervention may be discrepant. So that is important to have in mind because it is not only -- you know, this is a planned experiment, you know, that in most patients involves intervention, involves, you know, a specific outcome. We have a controlled treatment.

But, you know, in this case, you standardize everything, except for the intervention. They are different types of RCT. Again, I just want to make my message here is don't look only at one particular aspect of methodology.

When you are thinking about, no, this is only one paradigm, I think do we have (unintelligible) actually a conclusion. We have in conventional medicine and scientific community actually the tools to do research in a good way. And the RCTs can be classified in different ways.

I realize this one's from Dr. Jadad's book -- RCTs according to the aspect of intervention they evaluate. They could be experimentory and pragmatic trials. More and more, I can see in the literature evidence of pragmatic clinical trials being done. In pragmatic clinical trials, I just want to let you know, the patients' preference are taken in account. People actually -- you are not interested in how much -- in how the treatment really work. You just want to know it really works.

You have efficacy and effectiveness trial. It is almost the same thing. But I believe that in -- I cannot go into the details, explain all this But the phase I, II, and III clinical trials are actually basics. In clinical trials done for drug development in conventional medicine, where you have the phase I, where you actually specify the dose is most likely in healthy people and see how they tolerate that.

In phase II, actually, you just want to see the outcome. It is very common in oncology to do phase II clinical trial of new treatments where you actually compare that to a standard treatment and see, you know, who of the patients -- I mean, you compare it to a standard treatment, a new treatment, and then you see how long was the response or the survival.

RCT's according to how the participants are exposed to interventions, again parallel trials, crossover factorial design. Thus all of these are very well explained and very well documented in the literature. And I just want to encourage you to know that these are available.

RCT's according to the number of participants, I believe that from n of 1 to megatrials -- and I think that an n of 1, it may have a very good applicability in many of the CAM therapies that I am aware of.

It is maybe, you know, going to motivate people who do research here to provide more of these wonderful designs for CAM and at the end at least continue the RCTs according to whether the investigators and participants know which intervention is being assessed.

There are open trials. There are single blind trials. There are double blind trials, triple probably, and you name it and it is really, really amazing. Some people are concerned about how you can blind, you know, this and this and how you are going to -- but, you know, it's amazing and you will see in the next slide the trials that people are doing in CAM.

Again, our RCTs according to whether the preference of nonrandomized individuals or participants are taken into account. There are different designs again, very well described in the literature.

Issues in the study design applied to CAM. Again, the type of study may be qualitative, may be quantitative. It may be specific, you know, pragmatic clinical trial. It may be an observational study. It may be a perspective, maybe a retrospective. We get that information from best cases. We get that information from anecdotal evidence. We may get that information from past experience. I mean, we get that information. We need to adapt the methodology to how the treatment is actually given, and that's a key thing here.

The definition of intervention -- again, I mean, at least I need to know how they administer that, you know, what is the best dose, what is the -- I need to have those tools in order to measure something. Population, of course, of interest again it's related to patients.

Assessment of results -- there are many ways to assess results in a clinical trial. And that is actually important. Some of this can be manipulated even before the trial begins, so you know what you are looking for.

Method of comparison -- you have to decide, you know, are you comparing with a standard treatment? Are you comparing with the best available treatment? Are you comparing it with a placebo or an inert substance? Are you comparing it to another therapy? I mean, that is stuff that needs to be specified right away.

Data collection and reporting -- again very important. And I add reporting because it is really important to report the results in a way that is understandable. And I recognize in the audience people who actually emphasize -- and I have seen in the exhibit -- you know, the reporting for patients. And that is really, really important. I mean, people are not really too much interested in, you know, well, all the details. But people want reliable information.

They really want good information, and that's the key. I mean, that is why all these people are down there presenting different ways to gather information.

An interesting question again, qualitative versus quantitative, individual versus group, benefit versus risk, field versus laboratory, patient's right versus other's right, maybe doctor's right, maybe nurses, maybe industry rights.

I mean, you have to think about this when you are actually thinking of CAM research, and empirical versus evidence based. I mean, history of medicine actually relies a lot on empirical evidence. Do we go for that or do we go for evidence based? That is something that actually is open for discussion.

Treatment effectiveness -- again the same thing, how the treatment is administered. I will skip this one.

Ethics -- I believe that ethics are equal anywhere. Exposing patients, I believe, to an intervention believed to be inferior to current treatment is unethical. I mean, I think it is unethical to force you to do something that you don't want to do. It is unethical to impose my own system on what you think is better for you. But I think that you will -- this ethical research and CAM research actually comes from the conventional research, respect for persons. Do no harm.

We're not going to expose people to a risk that could be avoidable, just as validity, value, honesty, accuracy. I really believe that those are the things that (unintelligible) was referring to when he was asking, you know, to be honest.

I just will go quickly now with the information about how I think and how I have to have been searching -- where are we, actually, in research in complementary medicine? I love this. I found this article recently published in the Archives of Internal Medicine by the group in the U.K. And it is interesting.

They did actually just a search articles on Medline, and they used different search terms for many alternative medicine. And in fact, you will see the actual squares, the black squares, with the same. The alternative medicine article -- clinical trials -- alternative medicine articles published between 1966 (sic) and 1996, in 30 years.

The total articles, the CAM articles index, actually, was only 0.4 percent of the total number of Medline released articles. The numbers actually are astonishing because of 8.55 million of articles in Medline, only 33,000 were regarded as alternative medicine.

However, between -- as you can see, between 1986 and 1996, there has been a change. And I will call that a paradigm change. You know, it is amazing, the amount of articles that have been published in the last ten years. And that reflects many things that I would like to discuss later.

But one of the things that I find more interesting is the fact that, you know, this is in the main line, mainstream medical literature. I mean, that reflects something. And I think it is actually -- where this is going.

Again, the clinical trials articles, as you can see, is very low, 2.1 percent per year, but has increased significantly from 1987, reaching around 10 percent of the total. So that is really interesting.

Medical -- I am not, you know -- this is actually what I did. I said, well, what about cancer, what about clinical trials of cancer? And I did a very quick and very simplistic and very simple research, Medline research by myself, and I say, well -- and you can see there. I just, you know, searched for alternative medicine clinical trial, alternative medicine articles, and you can -- and I agree, my small research, uncontrolled research showed that, as Dr. Ernest (unintelligible)'s paper, the number of articles has increased steadily from 1966 up until 1997.

I actually went over to the year 2000. And I want to emphasize here that I was pleased to find many different clinical trials on cancer in the year 2000 that were just published, I think, in January, February and March. And that is really interesting.

Again, clinical trials still are a very, very small number in that particular -- in the number of publications. Clinical trials on cancer are a even lower. I mean, there are no clinical trials on cancer in the first three periods, actually. But between 1997 and the year 2000, I found 13 clinical trials on cancer.

So it is interesting, you know, from zero, for the past 30 years we have got to something. Again, I mean, this only reflects the fact that researchers are interested in this, that people are asking for the information. And I believe that we can improve this a lot better.

Again, I mean, I don't have time to go through all of the details of the details on this one. But I just want to emphasize that there are, you know, thousand of review; not thousand, hundreds of the reviews now on alternative medicine, and most of are worth looking at.

In terms of research and in terms of papers published, there is always a critic, you know, oh, they are not very good. They have to be improved and I think that that is what we are here for.

I really believe that the only way that we can have to get the information is getting together in groups like this and talking out and speaking out what you feel needs to be done.

These are actually critics so that people have said about that (unintelligible), but it is too much variability, that the observations are being too short, that there is combination, and you never know whether -- what is the treatment that really worked, and there is a reporting bias, that there is the measure was inadequate. And I think that this is critical for CAM research, but to be also applicable very well to conventional research.

Again, I hope that at the end of the day we all can talk the same language and we can understand each other. I don't think that we are too bands here. I do believe -- and I go back to Mimonides. You know, I do believe that we only have one goal, which is the caring and good caring of our patients and to think about it.

I actually have these slides available to everybody. These are actually five or six quotes that I would like you to read. People sometimes look for the wrong data, either wrong data, or make one inference on the basis of their understanding of the data. That's a good thing to think about it.

In an effort to gain knowledge, we have less information. RCTs can tell us which treatment is better, but they cannot tell us for whom it is better. People learn from stories. Institutions learn from data.

To interpret the result of a study in a meaningful way requires the people who are being studied to tell the investigator what results are meaningful to them. I think that those are really things that need to be considered in CAM research.

Again, I roll out this slide for a friend of mine in Germany who is doing (unintelligible) research. And actually (unintelligible) research (unintelligible) I actually want to apply to CAM research.

I do believe there is story with an open end, and we are here today, hopefully to start writing that. Thank you very much.

(Applause)

DR. SAGAR: Thank you, Carmen. I'd just like to say so far that clearly we can see there is lot of flexibility built into the research system, depending on the question being asked. Clearly, the whole point of research is to avoid bias and also to determine which subgroups our particular therapies are effective for.

Alex Jadad. Dr. Jadad is chief of the health information research unit and director of the McMaster Evidence Based Practice Center. He is a professor of clinical epidemiology and biostatistics at McMaster University. He has contributed enormously to the methodology of evidence based medicine.

His clinical practice is in pain management and palliative care. His latest research focuses very interestingly on patient information resources and the Internet. Thank you very much for coming, Alex.

DR. JADAD: Thank you for the invitation. And you'll have another round of Spanish accent here.

(Laughter)

DR. JADAD: I live in a kind of limbo, I think, most of the time. Coming from South America, working in Canada, trying to do palliative medicine that is one of the recent health care with the lowest number, I think, of randomized trials, surrounded by epidemiologists and biostatisticians, being a patient advocate, playing the role of a physician most of the time.

I have worked in three countries, England, Canada, and Columbia. In all of those three countries, I have seen the pressure of practicing evidence based decision making.

So I ended up at McMaster University, that for some people is called McMecca in evidence based decision making, is like the palace of the randomized trial. Then I was invited to write a book by The British Medical Journal to be launched at the 50th anniversary of the randomized trial in medicine, a pretty big honor for a Columbian working in Canada.

I started writing that book, and they asked me to write it in a way that people could understand. I had Dr. Murry Inkin (?), who is an obstetrician, for those of you in the audience who have children and have had a father in the room and didn't have your perineum shaved and didn't have an episiotomy, you have to thank him.

He is a 76 year old man who used to read each of my chapters. When I was right, I would say, half way through my book, he said to me, you know what, you are Catholic. He is Jewish.

He said, I look at you as a priest who has been asked to write a book on theology and doesn't believe in God any more.

So I wrote this book on randomized trials. And by the end of it, I was really sad of the conclusions I was reaching. So today -- and I learned many lessons, though, I will try to share with you.

I will start by setting the scene of what randomized, controlled trials are. They are regarded as the gold standard to evaluate health care intervention.

Regardless of what you think about them, people are going to ask you is there a clinical trial on what you are trying to propose. Oh, but it is very difficult in CAM and all that. Show me the data. In God we trust, but you have to bring data. That is the response you are going to get from most people, and even if you don't believe in the value of randomized trials.

And I think it is smart if you learn all the mistakes that have been done around the use of randomized trials so that you avoid them, even if you invent a new method to study complementary and alternative therapies.

So randomized trials have been used extensively for 50 years, and extensively are using a second -- what I mean by that -- and they are usually at the top of most systems to grade evidence. And Carmen Tamayo just showed you the levels of evidence and randomized trials are usually at the top. So if people want to believe in something and approve something and pay for something, they may do it more readily if you show randomized trials than if you don't.

But during the past ten years, I have been fortunate enough to be part of a bunch of rebels, I would say, that have been looking at randomized trials as the subjects of research, not only as the tools for research. But can study that to see where we are?

So what lessons have we learned from empirical methodological research and randomized trials? This is research that uses the clinical trial as the subject. Studies look at patients as the subjects, this bunch of people. (Unintelligible) is one of those. Has been looking at the randomized trial, as the subject of research.

So lesson No. 1 -- and I am going to walk you through nine today. The first one is that randomized trials have helped us evaluate many important interventions and detect small to moderate effects, both beneficial and harmful, of those interventions. You don't need randomized trials if the effects are evident, okay? If you are convinced that something works and the patient is convinced that the treatment works, it is extremely difficult to design one.

To detect big differences, you don't need a randomized trial. But they are done because we are running out of penicillin examples or insulin examples. We are really trying to bring incremental amounts of benefit. And they are at very small and frustrating trials sometimes. You need lots of people and be very careful to make sure you don't miss a difference when there is one and you may have had no time to see that one.

How many randomized trials do you think we have done in the last 50 years? Lots for sure, but how many? Okay. You see, there is evidence that more interactive the presentations, the greater the amount of knowledge that remains in your head, especially after half an hour, okay, being sitting there. So give me a number, everything and everything.

AUDIENCE MEMBER: A hundred thousand.

DR. JADAD: One hundred thousand.

AUDIENCE MEMBER: Ten thousand.

DR. JADAD: Ten thousand. One thousand.

AUDIENCE MEMBER: Five.

DR. JADAD: Five thousand. Five or 5,000?

AUDIENCE MEMBER: Five.

DR. JADAD: Five.

(Laughter)

DR. JADAD: Okay. One, two, three. The Cochrane Collaboration, which is a group of over 5,000 people working mostly as volunteers throughout the world to produce systematic reviews; these are scientific reviews of evidence.

In other words, we have a problem. We gather all the clinical trials around that problem and try to come up with a bottom line, does it work the same. It doesn't work, how much does it work?

They have by January of this year identified 268,000 clinical trials in the whole of health care. In my field of pain relief, I work with 12 volunteers, and we searched by hand 1.5 million journals and pages of journals, 1.5 million pages, and we found 8,000 randomized trials in pain relief alone between 1950 and 1990.

Since 1990, we have doubled the number of randomized trials in pain relief alone, okay? So this is growth. It has 268,000 clinical trials in the whole of medicine, and pain relief, which is a very important area for CAM, is doubling the number of randomized trials in less than ten years, and that has remained the case since 1950.

So first of all, lots of trials. Lesson No. 2 is that very few of them really address important issues, more than 90 percent. When I don't feel like having a good day, I say more than 97 or 98 percent of trials, sometimes 99 percent of trials are a waste of time from the point of view of the clinicians and the patients and the purchasers, a waste of time. And for some people, this is waste of life.

So the reality, we have lots, and we put the randomized trial on a pedestal -- is that most studies are designed to meet the needs of researchers and regulators. You have these people trying to become professors very quickly and travel the world giving lectures. They have to publish, otherwise they perish. So they come up with these things, okay, and we publish them.

Who cares if they are important to patients and people trying to make decisions, and regulators. This fixation with a placebo controlled study is harming lots of people. I think we need to be concentrating more on pragmatic trials that are trying to show us if the new intervention is better than what we have.

We have little data on issues of interest to clinicians, as I said, patients, and purchasers. For example, we have very few head to head comparisons of things. We have the new thing versus the placebo. Okay, yeah. Do you think a big company or a big research group would be comparing something with a placebo because you know it was going to beat the placebo? So surprise, surprise when it does.

The key issue is this is better than what we have already. Very futile, very frustrating. And I have done over 200 systematical use already in many areas in health care. The most frequent answer or conclusion I get in my papers is we don't have the right comparisons, okay? We really don't know if the newer stuff is better than the old stuff. People haven't been asking the right questions.

There are few efforts to measure satisfaction with care, adverse effects, quality of life, resource relaxation, things that are the really important ones from the point of view of the decision makers. And who cares about what patients think and clinicians? So we don't give them the opportunity to have input in the design of the studies, correct? We know best. I think this is a tremendously important problem for clinical trials.

When I as a clinician look at the papers, I say, my goodness, why did they measure that? I can't even describe that rotation. They would laugh if I told them what was measured. And when you look at most of the regulatory efforts, here is what happens from the perspective of the investigator. They try to select the most promising compounds based on instincts, mainly. There are very few organizations that follow a very systematic process to identify the best winners.

There are excellent phase I or phase II trials. These are very small exploratory studies in which you are trying to have a feel for what is safe, what is the most effective dose. Then you are jumping to phase III trials. There are those that are trying to show if the intervention is better than a placebo, basically, which are usually of short duration. They compare the intervention with the placebo, and then that is sufficient. If you show that something beats a placebo once or twice in some countries, then you are ready to put a dossier ready for the regulatory agencies.

Then after you have the drug, the compound, approved, you put all of the marketing people behind the product to ensure that everybody knows about it and gets into the radar screen of the prescribers and the patients. By the way, now there is more direct-to-consumer marketing done, direct-to-physician marketing, and then limited and defensive research after approval.

So once the drug is approved, most of the efforts after that has been marketing. And if you do research, it is because somebody attacked the drug. They were trying to disprove what somebody said.

The idea, however, in a realistic study, should be, And this is what I would recommend you to do, if you were doing research in CAM, is that you have a systematic selection of the most promising compounds. You make one step after you are more comfortable with the previous one. You do excellent phase I and phase II trials if you want to do randomized trials. Then you do excellent phase III trials if you are believing in randomized trials, comparing the intervention with placebo and the best available alternative.

Then you need to ensure if you are forced to do randomized trials and you do them, then you can create a dossier for approval based on evidence of added value. If you want to sell the stuff, okay, heavy marketing after approval, but then proactive research after approval.

I think after most of these compounds go to marketing in the traditional world, it is sad to see that all the key questions remained unanswered.

DR. JADAD: They call messages is the "so what test," okay? If you have something, think about this. This is what I do, and I read less than five articles in Pain Relief every year, less than five. For me, it is easy to keep up-to-date.

The first question of the "so what test" is does it work. You have something new. Does it work? And that's the placebo versus the active type of thing, or even if you have patients tell you that they are delighted with it, and your colleagues are reinforcing that.

Is that enough? I don't think it is enough. You need to answer the second question, is it better than others out there? And that can have different forms. The first one isn't as effective than what we already have, but safer. Is it as safe but more effective? Or is it as effective, as safe, and cheaper? Perhaps this third one is one of the most attractive for many of the CAM therapies.

Even if you answer this, the question is, is that enough? I don't think it is enough. The key issue is, is the effect worthwhile, or is it just small, or you cannot replicate it, and you need to spend who knows how much time trying to get it, or how much training and so forth?

But this is really the "so what test." If the intervention passes the "so what test" regardless of what techniques you used to measure it, really randomized trials, then you are fine.

Lesson No. 4 -- most trials are prone to bias. So the previous one was that they really don't answer important questions. Even when they are trying to look at important questions, they are very vulnerable to bias. I will give you some tips here, and I will not spend -- if they are published in English, as most of them are, they are more likely to show positive results. If they are done in some countries (unintelligible), particularly China, Russia, Taiwan, I believe Poland, I think, they tend to be more positive. Use crossover designs for conditions that can be cured.

Crossover designs are studies in which each patient gets the same treatment -- gets all the treatments that are being compared. So during one round, you get treatment A, and the next round you get treatment B. But if you are dead, you cannot go into treatment B. If it is something for infertility, okay, and you get a baby, you cannot go into the other.

The surprising things is that 20 percent of trials in infertility are crossover, okay, and they can exaggerate treatment it takes by up to 74 percent.

If they are funded by the manufacturers, people delivering or developing the interventions, they are more likely to show positive results. In this case, you may be the manufacturer of such interventions, so you need to be very careful. I am my worst enemy. When I wake up, every morning and say, okay how am I going to deceive myself today? We are very good at that.

(Laughter)

Then another message or sublesson is that even within the same specialty and the same language and the same discipline -- these are obstetric trials in obstetric journals in English -- you have a huge degree of variability in the quality of the studies that they published, measured with the same method. So it is a big mess out there.

Industry funding -- funding of the studies by the developers of the intervention, a key issue. And this was a paper that won an award in 1996 for the best paper for the International Journal of Technology Assessment in Health Care. And (unintelligible) Lisa Bellows(?) just showed that studies have found consistently that industry support is associated with poor methodology and results that favor the sponsor's drug. I think that you could be regarded as the manufacturers of the interventions and the proponents of the interventions.

The studies and supplements have lower quality than those in peer reviewed journals. Forty-three percent of drug trials favoring new therapy were funded by industry versus 13 percent trials favoring traditional therapies. So you see, there is a huge effect from industry on that. But even if industry is not involved, trials are very vulnerable to manipulation. I want to highlight some of the elements that make a particular issue especially vulnerable to manipulation.

The first one is if you have different interventions belonging to the same group with wide variations in practice. If you are thinking cancer, this may be different chemotherapeutic agents. Think of different types of chemotherapy. There's a potentially huge financial gain or loss for industry, depending on whether the new treatment is effective or safe.

Then one of the key ones, okay, if you have an ambitious researcher with unfulfilled dreams of fame and wealth, and sometimes journalists; I have another slide with journalists. If you have ambitious journalists with unfulfilled dreams of fame and wealth, then the potential for manipulation of information is huge. There are studies showing that journalists favor positive results. And we find cures for cancer almost every week, okay?

The patient is desperate for a cure, another important element to make research prone to manipulation, but with no input in the research process, and the government or health care provider desperate to cut costs. And I think cancer meets all these criteria.

So the potential for manipulation of research around cancer, traditional, conventional, or complementary, alternative, is huge. This is one of the most frequently used approaches for manipulation. I call it the self-fulfilling prophecy.

You have a drug and this is increased the dose. You can increase the amount of benefit, up to a point. If you keep increasing the dose, it just flattens. But then what happens with safety with something like this, with adverse effects, adverse events? You can increase the dose, you have very few side effects and then as you increase it, then they go right up.

You have two drugs, A and B. You give A here; you give B here. Guess what the conclusion of the study is? A is better than B, okay, while in fact they may be very similar. You just give a little bit more of B and put it into the unsafe territory. This is used many, many times in conventional research. And like these, I have many, so I don't want to spend too much time.

I just want to bring my friend Alfred Hitchcock, who used to say that the perfect crime happens every day. It is perfect because we don't notice it, okay? It is so well designed that we cannot pick it up. I think there is lots of that going on out there, big organizations, small organizations trying to prove a point. There are some very creative strategies to make sure that nobody notices. I don't even think he wrote this, by the way. He had a ghostwriter, so even he missed it.

(Laughter)

But anyway, lesson No. 6 -- Even if perfectly designed, clinical trials can indirectly lead to biased decisions. How important is publication bias? Publication bias means that you don't publish what you don't want to be published. So the trial is perfect, and voila, you show that a new treatment doesn't beat the existing treatment or a placebo. You don't send it to a journal. Or if you send it to a journal, the editor doesn't want to hear that or the peer reviewers. The paper never sees the light of day. Big problem.

We have been trying to fight it for years. And only two countries, Finland and Spain, have compulsory registration of clinical trials. Even here in the U.S., we don't have compulsory registration of trials from inception. So nobody knows what trials are going on. It has been extremely difficult to get investigators to document what trials they are doing, and ethics committees and I think this is a great disservice to patients because --

AUDIENCE MEMBER: ———

DR. JADAD: Sorry?

AUDIENCE MEMBER: Which two countries?

DR. JADAD: Spain and Finland. There may be others now. But I went to Spain and congratulated the audience. I said, you are one of the countries in which trials are registered at inception. Bravo. And somebody said Alex, do, you think that works here?

(Laughter)

DR. JADAD: Okay. So I am going to ask my Finnish friends and see if it works there. But again, it would be ideal, you see, if you are invited to be part of a trial, but you as a patient know that that trial is not being done somewhere else, or it hasn't been done, and shown that the treatment is a waste of time, especially if you are dealing with cancer.

It is unethical (unintelligible) called it unethical not to publish the results of any research done because patients expect the results of the studies to be available to them and to others, especially if the treatments don't work or are harmful. Yes.

AUDIENCE MEMBER: What do you mean by registered?

DR. JADAD: That's right from the beginning. It would be of use to have a database that told me somebody is comparing painting, I will call it, (unintelligible), a substance that comes from wall paint, I don't know, versus placebo. And then after that, we have documented that negative studies can take twice as long to be published as positive studies.

What I am saying is it would be ideal to know what has happened and what is happening now to ensure that the next decision is based on that and not that we are duplicating efforts or putting people through unnecessary risks.

And the interventions are multiplied by reader biases, okay? We are human beings. We are wired in peculiar ways. We believe what we want to believe. We see what we want to see, and we listen to what we want to listen to.

Rivalry bias -- you hate somebody, you believe the research less, okay, than if you loved him. Territory biases -- okay, you want to be the king of the pond here, and somebody comes and does something, forget it.

Do something bias -- okay, there is nothing we could do, and there is something that appears to be useful; so let's do it. Let's believe it. Prestigious journal bias -- New England Journal of Medicine, amen, okay?

(Laughter)

DR. JADAD: Famous authors and institution bias -- Memorial Sloan-Kettering, it must great. Belligerence bias -- I don't like anything, okay? So I don't care who it was, where it came from and it just goes on and on. We have a collection, and we'll share it with you later.

Lesson No. 7 -- most studies are reported incompletely. Over 95 percent of randomized trials are poorly reported. Many efforts have been made to try to improve this, and they have basically failed. The latest and perhaps strongest is the cancer statement.

This is a group of international investigators, authors, and peer reviewers who got together to try to come up with criteria that people could use to improve the quality of reports. And the url is www.cancer-statement.org. And I should have put it bigger there.

But improving the quality of reporting will not be easy. Only about 80 journals have adopted this statement, even though it was published in 1996 in JAMA, 80 journals, and we have over 50,000 in medicine, 80 journals.

I heard that the Vancouver group that includes the top journals in the world decided to adopt it, like last week. But it was published in 1996, and only 80 journals up to last week out of 50,000 have adopted those criteria.

Lesson No. 8 -- most trial reports are boring, boring. That is one of the greatest problems we have. Who would pay attention to them? They are cryptic stuff, full of jargon, impenetrable sometimes. Boy I don't know why we read them.

I sit by my kid, and she is reading her report, and I'm sleeping with a journal. She says, Daddy is yucky. She is right. So you have a great opportunity to start writing your pieces of research in nice, attractive ways. We have wasted 50 years of writing paper (unintelligible).

Lesson No. 9 -- just to summarize, there is a gap between methodological research and methodological practice. We know how research can lead to a minimalization of bias. We know what the characteristics of a report should be. We know about sample size, how many people we need to study to achieve a meaningful answer, and yet we don't do it.

So bridging this gap would require incredible effort, and we haven't been able to do it with almost any strategy I know of.

So I would like to quote one of my favorite papers. And I practice evidence decision making. I'm the director of McMaster evidence based practicing. By the way, I don't think it is making any difference. But we need to think of medicine based evidence. So when you are designing your studies, think of the uses. Don't think of just you trying to make a point and prove yourself right.

Make sure that your studies are going to satisfy the needs of those who are trying to make decisions in the frontline. Otherwise, you are wasting your life, and others.

I would like to conclude and give you access to -- I heard this program. Therefore, it is the only commercial link that I declared in the program. That is free. I donated it. I was getting like \$1 per book. So I said make it available on the Internet. So my book is available free of charge on the Internet. If you want to buy it, thank you very much. Think of me. One dollar will be who knows what with that.

You can have access to it, and most of what I said today is there, okay, including the classification of trials that Carmen described before and Andrew Vicjker's paper. Okay. So thank you very much.

(Applause)

DR. SAGAR: Thank you, Alex. As provocative as ever. By the way, Alex, I think you should start using a Macintosh as well because you do think differently, which is what Andrew is doing now. So is it set up in Macintosh?

DR. VICKERS: Yes.

DR. SAGAR: Andrew Vickers, Dr. Vickers, received his doctorate from the University of Oxford and has been the principal investigator for multiple randomized trials and systematic reviews, including the papers on CAM. He is an author of papers on research methodology. He is editor of the journal *Complementary Care for Medicine* and advisor on CAM to the Cochrane Collaboration for Evidence Based Medicine.

He is also an author of five books, including *Examining Complementary Medicine*. And although he hasn't lost his accent yet, he is currently researching on CAM in Barrie Cassileth's department at Memorial Sloan-Kettering in New York. So thank you for coming. Welcome, Dr. Vickers.

DR. VICKERS: Some people were talking yesterday about coffee enemas as a treatment for cancer and having listened to Alex's talk, I now know what it is like to get one.

(Laughter)

DR. VICKERS: No. That was a fabulous talk. I'm not sure I can top that. But just to tell you what I am going to talk about, this is who I am.

I'm at Memorial Sloan-Kettering. You probably heard of it. It is the largest private cancer center in the world, and it is important in the development of cancer treatments, such as chemotherapy, radia- therapy.

I'm an interesting appointment. My permanent appointment is Leeds School of Medicine. I also have a secondary appointment in biostatistics and it's coming to a point I'm going to return to is I'm going to integrate complementary medicine into conventional cancer. That integration is not just at the practice level. It is going to be at the research level, too.

Just to tell you a little bit about what we do, we provide complementary therapies to cancer patients. Largely what we are doing is looking at qualities like anxiety, depression, fatigue and pain. We do have both inpatient and outpatient. I have been around with a nurse giving a foot massage on the wards to a patient in severe pain who is also on a methadone drip. If you wanted a photograph of integrative cancer care, I think you would have it right there. this is a large service, 1,000 patients or so per month.

We also have a research side, which is really what I am involved in. Part of the research -- I have to say as a caveat to start with, it is a brand new program. I have only been there six months, and most of the research I am talking about is planned rather than ongoing. But we are

going to do some studies of complementary medicines for things like anxiety and massage for pain, with music therapy for the intense stress and anxiety associated with bone marrow transplantation.

The main thing we want to look at, the main thing I want to talk about today, is botanical herbal medicines, substances like plants and fungi at the survival endpoints in cancer.

This is what I'm going to do. I'm going to first of all ask this question about why do research. This is a big issue in complementary medicine. You have heard about phase I, II, III trials. I am going to do in a funny order and start with phase III trials, and say, well, what do you need to know before we get into a phase III trial. We need to know something about phase I and phase II and my final point in preparation, please go out and do research, you know. Don't come to these meetings and say, well, that is very interesting.

We've have actually got to move forward because this has been repeated over and over again. There is very little reliable information for patients to make informed decisions. You know, if we walk around this exhibition hall, all of this therapy's is out there; how many of those have been subjected to randomized trials? I think very few.

So firstly, the question is why do research? To me, this is quite simple. If anyone wants to give me an answer to these two questions, has everything ever said by clinician about cancer been in the best interest of patients? No? Can anyone give me an example? Conventional, complementary therapy that has been promoted or proposed for cancer that is not done?

AUDIENCE MEMBER: High dose chemotherapy.

DR. VICKERS: High dose chemotherapy, right. We just recently with bone marrow transplantation -- widely promoted, probably doesn't work now.

AUDIENCE MEMBER: ——

DR. VICKERS: Right. Radical mastectomy is another good example, that you have to take out the whole breast and most of the chest as well. But, I mean, just to concentrate on the breast cancer example, clinicians doing that -- is there anything we can identify about those clinicians that were promoting this that is different from other clinicians that care deeply about cancer?

AUDIENCE MEMBER: ——

DR. VICKERS: So the clinicians promoting bone marrow transplantation and high dose chemotherapy were different from others?

AUDIENCE MEMBER: ——

DR. VICKERS: Well I work with Sloan-Kettering. The guys there make a lot of money, believe me. What is the difference between those guys and everyone else?

AUDIENCE MEMBER: I think that there is a belief that the only way that we can know —— of research, and that short of that is all opinion.

DR. VICKERS: Right.

AUDIENCE MEMBER: So the belief is that it is only —— half way that we come to on anything. And we both acknowledge only for a small amount done —— the next good thing that we all know about comes along.

DR. VICKERS: Okay.

AUDIENCE MEMBER: —— that says the only —— science.

DR. VICKERS: Sure. I mean, the point I'm really trying to make is that the people who have this -- you know, the people who promote therapies that don't work are no different from anyone else. They care just as much about cancer. They have dedicated their lives in exactly the same ways that we have to alleviate some patients' suffering.

The point is, we all make mistakes. You know, as Alex says, he wakes up every morning and thinks how am I going to fool myself today.

The fact that we genuinely, truly believe, and that we are careful in what we do, it doesn't insulate us all from making mistakes.

And I'm just going to go very quickly because I'm sure most of you are very well aware of what ineffective treatments in cancer has worked. The first one is did the patient really have the disease. A lot of these cures from cancer, we don't have any documentation, at least pathological confirmation, that they actually had a cancer.

We often hear in the lay press, the doctors told me that I was going to die in six months, and here I am ten years later. But prognoses are notoriously unreliable and often doctors are actually very bad at making prognoses.

I have noticed this particularly in complementary medicine, instead of talking about the results of randomized trials, people say, well, this works because inner cell study of NK447 breast cancer cells, there was a 27 percent reduction; or in an animal model, mouse carcinoma 180, the mice who had gotten my particular product had a lower tumor rate than the others. And because it works in cells and because it works in animals, it doesn't necessarily mean it works in humans.

Can anyone give me a guess at the -- you know, this is just from conventional medicine. How many drugs work in cells and animals and also in humans? What proportions will work in humans? Is it one in ten, any guesses?

AUDIENCE MEMBER: ——

DR. VICKERS: Ten percent? Anyone else want to give a percentage? Less than 50 percent?

AUDIENCE MEMBER: I think you have to define ——

DR. VICKERS: Okay. I'm sorry.

AUDIENCE MEMBER: ——

DR. VICKERS: We are talking about drugs that have significant and important effects in cell culture and in animal models. What proportion of those go on to show good effects in humans?

AUDIENCE MEMBER: One percent.

DR. VICKERS: One percent. It is actually about 1 in 300. So it is significantly less than 1 percent, okay, which is probably disappointing because every research proposal we write up, we say, oh it was fabulous effects in cell cultures, and exquisitely sensitive but it doesn't mean you are going to go on and actually go on and do human trials.

And unfortunately, a lot of the human trials that are done are done in tumor response. Well, the shrinkage of the tumor doesn't actually mean anyone is going to live longer. These are surrogate markers of efficacy.

I just want to say a little bit. In cancer, generally speaking, we are talking about how long people live. And it just turns out that the survival endpoint is statistically very complex. It doesn't have the normal distribution of bell shaped curve. It has what is called an exponential distribution and you have this problem of censoring, in other words, one dies. So how long were they going to live, or what happens to the patient you didn't keep track of.

You have got some data because you know they lived a certain amount of time. But then what happens to them afterwards? Any claim about a drug or an agent or a procedure working in cancer is implicitly a claim about survival, and it takes place in the context of the statistically complicated outcome of survival.

You have terrible selection bias. People rarely document all their cases and, of course, many patients drop out. They don't come back. The patients tend to drop out are the ones that do worse. So clinicians will tell you about what is reported in the literature, the most unusual, dramatic cases that respond. I mean, they might treat hundreds of patients, but the one patient who had a dramatic response, that is the one that gets published.

Also coincidence, say if I had cancer, I wouldn't just choose one perfect treatment. I would get a number of different ones. This is what most patients do. Very interestingly, most patients don't tell their doctors that their using complementary or alternative medicine, and vice versa. They don't necessarily say what drugs they go on.

I was recently involved in the case of a woman who had an apparent response to an herbal medicine and it turns out that she was also taking a hormonal therapy that was not actually revealed to the herbal practitioner.

So you have got a whole lot of reasons why an apparently effective therapy might turn out to be ineffective. The background to that is that when you are doing clinical practice, your job is treat patients, not to collect data. Data is gathered unsystematically, and unsystematically can lead to error, to mistakes.

So what we are trying to do in research is to use methods that were designed very carefully over many years of trial and error, a systematic design to avoid error.

I just want to very quickly go over this, what I think is a bit of an old chestnut. Having established we need to do research, do we need alternative research and alternative medicine?

I think the overwhelming feeling that most people who have been looking at this the way I have for many years is what drives your research design, how you choose this type of research, this question you are asking, not the therapy. And the debate that went on was extremely sterile.

My best evidence for this is since the early '80s, when this debate first started, the number of informative research papers that have been published on alternative medicine using alternative methods is almost zero. It hasn't really been fruitful. And it is a very '80s debate.

DR. VICKERS: Okay. Phase III trials -- basically, this is what Alex was talking about, was the definitive trial. Definitive -- if the result works, it works. If it doesn't work, it doesn't work. That's what we mean by definitive.

Also, as I have pointed out, we want to randomize. That is what we do, preferably. One thing that he didn't show, but he alluded to, is that this isn't some theoretical thing. This isn't a bunch of old guys sitting around the university saying, well, we really think the best way of doing this is randomized, and everyone has to toe the line on this.

There are empirical reasons to randomize. You can study trials that are randomized, and they have different results than ones that aren't randomized. You can study trials that are randomized well and have had ones that are randomized poorly. There are empirical reasons. There is an empirical justification for randomized.

The problem is, particularly in cancer, you can't always randomize. Some regimes, for example, the Gerson therapy, involves a lot of mineral juices. You have to go to Mexico. You have to have coffee enemas, and a lot of people -- In randomization, there is this assumption that you don't care really one way or the other. And most cancer patients will have very strong feelings about very unusual ratings such as that.

There are alternatives. And one my boss, Barrie Cassileth has been involved in is called a match case controlled study. What she did there is a very popular cancer center in the '70s and '80s called Livingston Wheeler. And what she did was a patient would enter Livingston Wheeler, consent to be in the study, and they would find some other patient from a conventional center who was similar to that patient, age, severity of disease, sex, age, and so on and so forth.

They would match them, so you would have these groups, and you would measure survival and perhaps also quality of life in those two cohorts.

That's where we want to get to, right? I'm going to assume that we have got all of these different approaches to cancer, and what we want to end up is some kind of phase III trial. Where we want to start is a phase I. This is conventionally what you do. Your question is what is the dose we are going to use in our phase III trial?

In conventional chemotherapy, you keep on escalating the dose. You give them ever higher doses until they can't take it any more and you say that is the dose you are going to use.

The reason is, is that in conventional chemotherapy toxicity is a surrogate for efficacy. If you give someone so much of a drug that it kills off their white blood cells, and they end up with clinically unacceptable toxicities as a result, you also know that drug is probably going to kill leukemic cells. So that is why we do it in phase I, in the conventional phase I.

I'm not going to talk about conventional medicine. You want to know what this is a picture of? This is -- sorry? Well, it is actually -- what the guy is doing is dripping a botanical medicine from the branch into the ear of -- I don't know who that person is, some forester or something. It is a traditional cure for earaches, and it is botanicals.

A lot of cancer drugs come from botanicals. And what is unique about all these drugs that have come from botanicals -- and I could list endless examples. The most well-known is probably the taxanes, which they derive from the Pacific yew, is you are only using one single compound. They are highly purified.

What we are interested at Sloan-Kettering is using whole botanicals. There are various theoretical reasons to believe that these might be more effective and/or safer as a complement to traditional chemotherapy.

How are we going to do a phase I trial of a botanical? And the important point, how many phase I trials of botanicals have there been, do you think, dose finding trials of botanicals? Do you want to make a guess? Fifty? Some people are saying none.

Well, if anyone knows of any, please do come up to me at the end, right? There are lots of phase II and even some phase III trials of botanicals. Mistletoe is a big example and we're trying does mistletoe work. But there haven't been studies to find out what is the right dose of mistletoe to give.

Part of the problem is the rationale for doing that hasn't really been worked out. Toxicity is unlikely to be high. Why would you give someone a drug until they couldn't take it any more?

And there are actually cases -- you have probably heard of green tea as a cancer preventative. Some people are interested in green tea as a cancer treatment. What we did in the phase I trial is kept on giving people green tea tablets until they couldn't take it any more. You didn't get any toxicity, but people were just bouncing off the walls from the caffeine overdose.

It is completely irrational to try and give somebody a botanical until they can't take it any more because the amount of botanical you can take is actually very, very high.

Similarly, you cannot assume a botanical works in the same as a chemotherapy agent. In other words, it doesn't poison everything and poison the cancer cell slightly more. So you can't -- toxicity -- why do you need to actually get the highest possible dose. And so you need to come up with some kind of alternative endpoints. And the three that we have come up with at Memorial Sloan-Kettering are pharmacokinetic parameters.

In other words, if you have some botanical that in the test tube, at a certain concentration, inhibits the growth of cancer, what you can do is you can take blood from a patient or a healthy volunteer and saying what kind of concentrations are we getting out of each dose.

You can look at biological endpoints. For example, a herb that is thought to have immune stimulant capacity you can measure interferon, interleukin, tumor necrosis factor. In other words, what is the biological response of the patient to actually receiving this particular herb.

One of the main methodological innovations that we are trying to develop at Memorial Sloan-Kettering is what we call *ex vivo* assays. We are going to take blood, either from patients or healthy volunteers, prepare it in a special way, and actually add it to cancer cells in a test tube.

If blood taken from people on an agent inhibits cells in the test tube, they not only have some clinical rationale for further development, but the curve, the dose response curve that you get can actually tell you the best dose to use.

So you have done your phase I trial. You know which dose to use. Let's go to phase II. Now in conventional, what you do -- this is just a single trial, no control group. The end point is response, a rapid shrinkage of the tumor ——— complete response where you don't have any tumor left, or partial response, where it shrunk maybe about 50 percent or so. We normally treat in the range of 20 to 50 patients. You just count the number of responses, the proportion, and before you start, you say, well, we would like at least 20, or 30 or 40 percent of our patients to have some kind of response. And if so, we go on to phase III.

What is the problem with doing that in botanical medicine? Well, firstly, I think tumor response is unlikely. The idea that you take the herb and in month you have a very rapid shrinkage of the tumor does not sound particularly plausible to me. We actually have empirical evidence now. Some of the botanicals we are looking at at my organization, from China, we have a very large case series, and very few of the patients actually had rapid shrinkage of tumor. So we need some other kind of endpoint.

So instead of looking at did the tumor shrink, we would look at did it progress. Or we could just look at survival. How long did people live? The problem with doing that is in the single arm trial, in the conventional phase II trial, where you are just looking at did the tumor shrink, you know what is going to happen if people didn't get the drug, right? Then the tumors aren't going to disappear.

So you have got an implicit comparison, whereas we don't actually know how many patients are going to progress or what their survival is going to be. So you need some kind of control group.

So whether you randomize or you use some historical control, when you are doing some phase II trials of botanicals, you are going to need some form of control group.

So we developed these what I call novel phase I and II designs. I'm not going to call them alternative because we are actually the methods. Most methods have already been quite well developed and I work with statisticians and other methodologists in the hospital to refine some of the methods that are already out there to adapt them to the problems of special methodological problems and botanicals.

I put this one out. Statistics -- it is very complicated, and it is really not easy to do that on your own. I'm in statistical department, and I get help from numerous other statisticians. And I think that is what really brings me on to my last slide, which is that let's not just talk about research. We actually have to go out and do stuff because there are patients there that need to make decisions, and there is very little information. Anecdotes, lab data, marketing.

Often, just as a sort of little lesson to myself, I go onto the Internet and type in cancer and herbs and see what comes up and imagine myself as a patient trying to wade through that information. You know, we really need to do something about that.

I have done research in CAM, and I think it is possible at this sort of conceptual level. I think it is practically feasible. On the question of practicalities, for many years people would talk about methodology and go to methodological conferences.

I think in CAM research, the issues are practical; who is going to do the research, what are their skills, who the lab technician is going to be, where we are going to get the statisticians from,

where the patients are going to come from. What about the research facilities to do ex vivo assays? Where is the lab to actually do that.

But I think if we can actually solve those practical problems, we are going to actually develop research, and we're going to come up with results that is actually going to benefit patients in their care. Thank you.

(Applause)

DR. SAGAR: Thank you, Andrew, for that very interesting and pragmatic advice. We have got about 15 minutes for questions. What I am going to do is put this program microphone up here, and then anybody who wants to ask a question, if they can just come up and use this microphone, please.

AUDIENCE MEMBER: Often in CAM we deal with complex concepts like stress and depression and social support and spirituality and things like that. Do you have or have you any experience with structural (unintelligible) or path analysis that measures -- that you can measure the causation of this complex phenomena?

DR. VICKERS: Well, to answer the actual question, no, I don't have experience in path analysis. But to take the first part, often in CAM we are dealing with complex phenomena like stress or anxiety or a number of other things you said. There are social workers at Sloan-Kettering that I work with. I don't see where the issues they are dealing with are any less complex than the ones that the ——— practitioners in my service deal with, or even the physicians.

You have to talk to patients near the end of their lives. I just think we have to be a little careful of making false distinctions of saying that the issues we deal with in CAM are much different from what is dealt with in conventional medicine. A lot of these issues have been dealt with quite well in the psychological and sociological literature. And I think there are probably things we can learn from them.

AUDIENCE MEMBER: Danton from New York. I really appreciated Alex's perspective.

I wanted to ask, in terms of your perspective, one of the things I think that is a methodologic problem is that having done alternative medicine and dermatology for 20 years, I make two diagnoses. I make a conventional diagnosis if the patient is (unintelligible).

But then I make an etiologic diagnosis. I believe it came from taking a drug. I believe it came from some combination of stress and some other series of things. And I try to address the etiologic diagnosis. And I kind of understand that.

That's how I learned alternative medicine, is that one goes and tries to address the etiology, not the disease. It is sort of more patient-specific. And I think there is a great -- there is a lot of nerve in saying we have a randomized trial and that we are balancing people because we are not balancing the etiologic diagnosis. We're usually just talking about the expression, the pathology that is there. And you can't assume that each pathology has the same cause.

So unless you go back and you try to randomize the cluster of data that seemed to lead to that condition and say, yes, we have two people who developed chronic fatigue after they had lyme disease or if they had a particular virus. It is going to change completely your approach.

So I think that that is not even touching the history of the patient and the genetics, which also add another set of variables. So I would like to see a better way of randomizing the etiology, saying yes, we have two people with the same etiology. What worked for them? So I just was wondering if that has been addressed by any methodologies that anybody has out there now.

DR. VICKERS: Well, essentially what you are talking about is treatment individualization. The patients come with a similar conventional diagnosis, but they need different treatments, essentially.

AUDIENCE MEMBER: Yes. By alternative or by --

DR. VICKERS: But I don't see that as a problem at all for the randomized trial. I'm running a very large trial in the U.K. at the moment. You know, two patients with migraine can get a very different Chinese diagnosis.

What we do is we don't care about that as a researcher. That is not my business. That is the clinician's business. What we are doing is we are randomizing patients, either to go to the acupuncturist or not.

They go to the acupuncturist, the acupuncturist can make any type of etiologic diagnosis, can treat them in whatever they want. What we do is after one year, we measure how the headaches are. We measure their quality of life, their resource utilization, and their drug intake. To me, in the randomized trial, there are no particular assumptions about their etiology or necessarily trying to find people according to etiology.

DR. JADAD: Yeah. But you can't believe strongly that etiology makes a difference. If it is not a traditional one, my recommendation would be to capture that information, and that later on see if, in fact, people who have specific etiological factors that you believe are important behave differently from those who do that. So I don't think those two approaches are incompatible.

AUDIENCE MEMBER: ——— The Chinese medicine ——— allows appropriate variables to address the situation ———.

DR. VICKERS: Just briefly, we'll mention this. But, I mean, there is a classic trial in Chinese medicine and in dermatology. It was the Chinese herbal medicine for --

AUDIENCE MEMBER: ———

DR. VICKERS: Well, what we did was they -- the type of the patient is interesting because it has something like widespread, (unintelligible) --

AUDIENCE MEMBER: The Chinese --

DR. VICKERS: They define the Chinese syndrome.

AUDIENCE MEMBER: Yeah.

DR. VICKERS: And they just randomize people with this particular syndrome. So, I mean, there are always of doing stuff.

DR. TAMAYO: Actually, I encourage you to go to the literature in the those 13 trials that I mentioned about cancer. Actually, if you read them closely, they do talk about that type of things. It is interesting. The methodology section is actually very well reported and how people have been randomized.

One particular that I found very interesting was the efficacy of homeopathic treatment of skin reactions during the therapy breast cancer, which I found particularly very well done, but interesting to see that they actually are doing things, even music therapy for children, for example. There is one on evolution of aromatherapy (unintelligible) care.

And these issues are trying to be addressed in these particular trials, which is interesting.

DR. VICKERS: I think it is true that most clinical trials do not record the patients' personalities and constitutions. They very rarely, for example, do a psychological evidentiary. It is a trend in intervention for organic disease.

For example, the case control study you talked about at Memorial Sloan-Kettering. You talked about the classics, you know, the sex, the age. But are they actually doing psychological profiles and matching those for those patients?

I think that we may find that that's probably an important factor.

DR. SAGAR: Just to mention that in some studies, we found that there were really only a few very significant factors.

I mean, sometimes you hear a story where there's been such a traumatic event. And it's clear you don't have to do much of a profile to know that, you know, the husband died in front of the wife, or something like this -- something really awful..

You don't have to be a psychologist to know there was a psychological event.

So, you know there was a very -- it doesn't take any sort of analysis. The other thing is that there have been people who have done some studies, like Dick Bergencamp (?) at the Cancer Institute. He had done a study back 20-some odd years ago when I was there on melanoma.

The whole MMCI (?) was administered, and people with really stage III melanoma. And he found only one ——— control ——— did it. And that was how significant they thought their melanoma is.

And once you thought, yes, it's significant, not the ones who pass through it, but ——— are the ones who are overwhelmed by it, and those people did best.

So, some of these kinds of things can boil down to really asking the really pertinent question. Now, you don't need to do huge profiles. You just need to go into the literature, and ask the pertinent questions.

DR. FISCH: Hi. I'm Peter Fisch (?), director of research at the Royal London Homeopathic Hospital. Just a couple of points, really, from our experience in the UK, bearing on your remark.

Certainly, one faces this kind of problem in homeopathic research. And what we've done, what I've done myself, is to take a given diagnosis, and then, to take the subset that meet the prescribing criteria for a particular homeopathic medicine.

And it works. The problem is, that you have to screen large numbers to get the numbers you need for your trial. But it can be done. The problem is the numbers.

One other thing that several of the speakers almost mentioned, is really, you know, this bootstrap problem we have, with so many complementary therapies. You don't know where to start.

Alex mentioned -- what was it about? Something about instinctive selection. How do you select for things? We, for about 2 years, have been trying to get a trial of a mistletoe preparation used for cancer, off the ground and it never quite happened. We were very frustrated, and we weren't quite clear why it wasn't happening, until we finally worked it out, that there was no agreement on how to use this stuff.

So, we put together a consensus conference, which was very successful. It was very healthy for the community all to get together and thrash it out. They actually did come to a consensus. We feel, we hope now, that that has actually, you know, dealt with the problem.

So, a consensus conference is something that we have found useful, you know, in this bootstrap stage. How do you get the thing off the ground in the first place?

Then just one word of caution, which Andrew I'm sure is very familiar with, and in fact, all the speakers probably are, about the case control study, the infamous case of the Bristol Cancer Help Center, which was a case-controlled study; appeared to show that patients who went to the Bristol Cancer Help Center, which is in southwest England, did worse than those who didn't.

It subsequently turned out that in fact, the thing that motivated them to go this center in the first place, was an adverse event. They discovered they had a metastasis, or something.

But the whole thing was -- it was published in the Lancet, a high-profile study. It was a horrible fiasco. There was no clear conclusion. It created a lot of dissonance and there was even a big court case over it. So, there are pitfalls to that sort of study.

SPEAKER: I am at Johns Hopkins University, where we are slowly, gradually trying to develop a center for the study of complementary medicine. Unlike Sloan-Kettering, we don't believe in service provision first. We believe in research first, and service provision later.

That means that, in order to do a lot of the studies, if we ever do get the center off the ground, we're probably going to have to collaborate with institutions in the general area, where there are CAM providers, because we don't have CAM providers, by and large, at Hopkins to actually offer the interventions.

So my question really has to do with how you deal with selection bias, I guess it is, or doing studies -- one of the places we're likely to collaborate with is the traditional acupuncture institute. It's so clearly a self-selected population. It's so different from the population that's likely to seek care at a place like Hopkins.

Is it a problem trying to do a rigorously designed study in a population that you know is unusual, compared to the population you want to eventually serve?

DR. VICKERS: Well, I mean, I first have to say that I can't let that comment about we believe in research first and provision later -- I can't let that go.

SPEAKER: I'm very serious. I'm telling you what they said.

DR. VICKERS: Well, I mean, the sort of things we're doing, massage for anxiety, for example. I mean, they're randomized.

Everything that we are doing, pretty much, is already based on randomized trials. Relaxation for anxiety, acupuncture for pain and fatigue, music --

SPEAKER: But who are the providers? You hire people to be the providers.

DR. VICKERS: That's right, yes. I mean -- I'm not quite sure of the question. Basically, we have -- excuse me?

SPEAKER: I'm saying that we don't -- I don't know about _____ but we don't have a substantial number of alternative providers _____.

DR. VICKERS: Right.

SPEAKER: _____

DR. VICKERS: Right. Well, there's a couple of points to make about it. I mean, there's no question we've, you know, hired in these members of staff. We have, you know, nurses who give the massage, for example. We have MDs who are giving acupuncture.

But your question about the patient population is, if you involve the traditional acupuncture center, you don't necessarily have to involve their patients. I think the basic model that is used, is that if you're hiring practitioners on a part-time basis to take part in a trial, they see your patients, not their patients.

So, the trial that I'm doing in the UK, for example, is patients that come from primary care at the _____. If they get randomized to the acupuncture, they go and see a local acupuncturist.

SPEAKER: Well, but those are two issues, though. We may also want to do a population-based approach that is not just focused on the patients who are very sick and think they're at hospice.

If we want to do research then we've got to have _____ involved on a more general population -
-

SPEAKER: _____

DR. JADAD: Yes. That would be my advice, and then try to recruit consecutive patients, and see which proportion of the patients you are inviting to be part of the study actually accept it and at the end, you can say 1 percent of patients invited to participate in the trial actually went into it.

That will give you a measure of generalized ability to be able to capture how big that group is.

SPEAKER: Two questions. What's your advice on needing control for attention; say in a guided imagery studied with kids? Do you believe you absolutely need a control where someone sits with the child for the same length of time, doing everything but guided imagery, just to pay attention?

The second thing is just a comment. We have designed sham treatments, sham qi gong, sham cranial manipulation, sham acupuncture. And what we've come to is getting them funded, and having practitioners absolutely refuse when push comes to shove, to participate in the trial, because of that.

So, I guess I'd just like a comment on that. But I'd like some advice on do you really believe you need control for attention?

DR. JADAD: I'm going to pass on both those, okay, because my role here is to try to challenge conventional research, okay, and to invite you to do things right.

So, my response would be yes, if you can. Okay? If you can have controls, have controls.

SPEAKER: Okay.

DR. JADAD: If you can have a good sham treatment, use it, because you are going to benefit at the end. Remember, I wake up in the morning and say, How am I going to fool myself? One of the best ways to fool myself is not controlling what I believe works, you see.

Because I am wired to believe that I am wonderful, you see. I am a nice person, that people love me, and nobody hates me and what I do is great, that my patients do wonderfully, that they tell me the truth, that my mother-in-law loves me, and all that stuff, you see?

So the more safeguards you can put, okay, to ensure that you're being honest to yourself and to the people you are trying to help, the better.

Sometimes, controlling things too much, spoils the soup. You understand?

SPEAKER: Yes.

DR. JADAD: Then that's where the trick is, is into ensuring that the art is not spoiled by the science. That applies to CAM and to non-CAM and that's a tricky business. But if you can do it and you believe that you're not going to affect what you're trying to measure, go for it.

DR. TAMAYO: I would think actually that, think outcome. I mean, I could agree with Alex's comment. We were talking, just in having the discussion, about how do you measure for a thing that cannot be measured? How do you control for a thing that cannot be controlled.

Look for the results. I mean, how you measure how ——— person may be? Well, see how is she doing in life. I mean, attitudes and changes, you know.

This morning actually it was mentioned, and forgive me. I mean, things like, you know, those things cannot be controlled. But actually, they may have an effect.

So, look for outcomes of the research that you are looking for, instead of actually looking for the best, perfect method to do that.

DR. VICKERS: I'm actually very relieved that Alex said what he did, because I've now got something to disagree with him with, because I was beginning to think, listening to his talk, "Oh God, I agree with everything he's saying," you know, which is very unhealthy.

DR. JADAD: I was getting worried.

DR. VICKERS: Yes, yes. Well, I think at one point, you said you actually can use a sham (?). I've just had a paper published, and anyone who wants to, you know, I'll get them the details if they come up afterwards, why you use placebos in clinical trials.

This was just published in the Journal of Clinical Epidemiology and the basic thing you've got to go back to is the question that you're asking.

What people say, should I use this methodological maneuver? I mean, these things do not happen in isolation. You use the methodologies towards the particular questions.

In placebo research, why do you use the placebo in clinical trials? Well, we analyzed the entire literature from the Netherlands.

Most of the reasons -- there were a lot of bad reasons. It could boil down to two things. One is to facilitate blinding. So the simple thing is, if the patient knows they're getting a treatment, they often give a more optimistic assessment.

Blinding is well-known. It's important. In your studies, it won't make any difference, right. Patients will know whether they're getting attention control or creative imagery, quite probably. The other reason is --

DR. TAMAYO: Oh, for sure.

DR. VICKERS: The other reason, really, that we found in the literature was to control for the placebo effect. It was completely inadequately argued why you have to do that in the methodological literature.

I think there are reasons to do it. But the reason I'm saying that, is, you know, we've dealt with this question. Do you need an attention control? Go back to the question you're asking, right.

If you don't do it, then people will say, well, it wasn't the creative imagery, it might have been the attention. Do you care? Right?

From a patient point of view, patient doesn't care. Right?

DR. TAMAYO: They don't care. Absolutely not.

DR. VICKERS: Maybe a provider does care, because maybe creative imagery is more expensive than just spending time with people.

From a scientific point of view, it's very important. I think in our textbooks, we need to know whether there's something special about creative imagery, or whether it's just a function of spending time with people.

So you can give a variety of answers to that question, is it important to know whether it's just the time and attention or if there's something specific about creative imagery. You can come up with different answers, depending on the question that you're asking.

DR. JADAD: Yes. I'm disappointed to say that I agree with you, and that I don't think you disagreed with me in the first place.

I'm doing research on acupuncture. I have a masters student whose most -- I think the greatest amount of his income comes from doing acupuncture and he is doing a masters in epidemiology. He's in a fantastic journey like ———. He just discovered this great paper on placebo acupuncture and he's planning to use it.

So the issue of if you can use it -- I was using CAM in the sense of if you have one available, okay, not in the ability to implement it in your practice or not.

I'm going to separate "could" and "should," or "can" and "this is a good idea to do it." If you just ——— trying to get the microphone back.

But one line that may have been lost, is testing for blinding. If you think you should use blinding and a placebo group in your studies, make sure that at the end of the study, the blinding was effective.

SPEAKER: Right. Okay.

DR. JADAD: In pain relief, I come from pain research, expectations of patients and researchers can even modify responses to placebo. The way in which you look at the patient, the way in which you sit there, you look bored in one group and very excited on the other one, may alter the results substantially.

DR. SAGAR: Okay. One more question.

MS. HALLER: Yes. My name is Susan Haller (?), and I sit on the NCAM Advisory Council. And I am representing consumers on that council. It was mandated in the legislation that consumers participate in the council.

I was very glad to have come to this, and to have heard your talk. Because I wanted to say a few things, and ask you both, Andrew and Alex, a question that I think is going to -- that has brought you together. I mean, I think you're both talking about the same thing, and that's the question, the research question.

I do not have a research background. I do not have a science background. I am a patient who went out and did my own research, and so on.

I have found a couple of things, and many things that you, Alex, said, rang very true about the research agenda, and CAM, which is now evolving, and which I hope all of us on the council can, in some way, influence.

But I have found, first of all, the question -- you said very few of the trials address the issues of importance to the main stakeholders. This is a problem. It continues to be a problem, in my view, from the research and from the grant applications that we receive.

Secondly is the issue of serving the need of researchers, as opposed to, again, the stakeholders. In fact, I wrote a paper for Dr. Straus when I first came on, bringing this up, which I didn't even know was an issue. So I'm glad to see that somebody else thinks it is.

But what I'd like you to sort of address -- my problem is how to try to move the agenda to ask the right question. We've had several issues on this that have arisen, and I'm trying to figure out a way to help focus it more toward what stakeholders are interested -- the kind of information that they really need.

DR. JADAD: Dear to my heart. Starting with the issue of patient or consumer participation. I really don't know what that means yet. I've spent the last 10 years of my life, trying to have meaningful consumer participation of what I do.

What I end up with, is a group of professional patient participators, people who have strong beliefs before they come into the room.

So we are facing a major selection bias problem with consumer participation. After 10 years, I get finally the same consumers, meeting after meeting after meeting, you see? It's like preaching to the converted. They become such experts in the subjects as other people in the room, with their own ideas and their own intentions of driving the agenda.

That's pretty worry. So I wrote a paper with _____ but she led this and it's in Health Expectations for _____. I would be delighted to give you a copy.

I mean, studies on how to ensure meaningful participation from the public, are very tricky, okay, because we don't even know how to make sure consumer participation, to know if we have it at the right dose, you see, at the right level.

So even the issue of participation is a tricky one. What I do, is the following. It may be something that could be useful to you or not. I have a group of patients and in fact, half of the members of my research team are members of the public. Patients and family members. I don't exclude them.

We select the questions together I let them go first and then we have a second stage. This indeed is great, this is not great. Then I say, okay, we select our menu of possible questions. They will invite people who are coming to our cancer center and organize focus groups.

We let an independent leader to run the focus groups and we don't let doctors interfere with the patients' focus group because they can end up steering the whole agenda.

So we have members of the public who don't have a stake on the issue to be the leaders of the focus groups and run them.

Then, once we get the conclusions from that, we have a service. We get 200 to 300 patients to give us feedback on whether it is really important or not, because we're trying to protect our _____ and consumers as human beings as well. They have prior beliefs, and they have agendas.

If we are not careful, just by having one or two consumers in a committee, we're not ensuring adequate participation. But this is an extremely complex issue that I would invite you to work on with me in the future.

SPEAKER: So, how do you then -- how do the researchers react to the product of all of this?

DR. JADAD: Well, first of all, we make consumers researchers and half of the members of my team are researchers, and they are members of the public. To be a researcher, you don't need to have Ph.D. or many letters after your name. So, by the very fact that they are experiencing in the problem, or very interested in formulating questions or finding the answers, we declare them researchers.

But they have, as I said -- and I hope I'm not giving too much of a long-winded answer. They are also human beings with an agenda and we need to be very careful. If I'm careful about my own agenda, to color the whole picture.

SPEAKER: Well, let me give you a specific example. If I'm generally a consumer, or particularly a cancer patient, I'm certainly more concerned about the outcome or the effect of a particular thing than I am on the mechanism of action on it.

DR. JADAD: Yes. That's okay.

SPEAKER: Okay. But that's not necessarily true of the research community. It's a question of which -- I mean, not that they're not both questions. Of course they're both questions.

But, you know, simply the order of, you know, sort of the order of the --

DR. JADAD: Yes. But then, who calls the consumers, you see. This is another huge area of manipulation, okay. Involving consumers is the politically correct thing to do, correct? By "consumer participation," we mean having at least one consumer in the group.

Those poor people come there, they think they have a say. They sit there, all these sacred cows sitting around the table, okay, talking -- using this jargon, and all these complex terms. What do you think? Do you agree? All the big professors said yes, of course.

So, if we are really talking about consumer participation, we need to look at consumer participation as an issue that really deserves lots of discussion, because there is too much tokenism, and there is too much political correctness, and lip service paid to it.

It's a complex issue. I unfortunately cannot give you an answer in 3 minutes. We're trying to develop methods to insure that they have and most researchers don't care about that, because it's just a nuisance.

SPEAKER: Yes, obviously.

DR. VICKERS: I'll just tell three quick stories. Firstly is that you're right, and I know you're right, because I've actually done research on this. I did a study several years ago, where we actually did qualitative research with patients, practitioners, consumers, a wide range of stakeholders.

We said, what would you want to know about this particular research field? On the basis of what they told us, we went and did a systematic review of the literature to see if the literature was answering the questions that people posed.

Largely, it wasn't. So I mean, that was a very rigorous piece of research demonstrating the point that you're making.

On the basis of that, I thought I'd want to involve consumers. Something very interesting happened to me when I was developing the migraine trial that I was telling you about, was that I rang the Migraine Trust, which is a consumer representative organization in the U.K.

I said that we wanted a consumer representative as part of the advisory board for our trial. They said "Okay, I'll put you through to our neurologist."

I said, "No, you don't understand. We want a consumer representative, you know, someone in your organization, to give the consumer's point of view." And "Well, we have a scientific committee that meets Tuesdays, please send us your protocol."

I think that was my first experience of involving consumers. There are two consumers on the advisory board of that trial. I suppose like Alex, that I think we really are at the beginning stages, and we don't really know what consumer representation actually means.

My final point and I'll let Alex have the microphone, is that -- what?

DR. JADAD: No, no, no ———

DR. VICKERS: Very right. Oh yes, I see. Is that I'm a very strong believer in consumer representation but I also would say, in some very new fields, particularly in research that isn't at the phase III level yet, researchers often do need some time to articulate the science, pretty much on their own for a while, before bringing consumers in.

That there has to be a basic scientific background. I think it can be very difficult to involve consumers at that very beginning level. Although I do believe strongly in consumers being involved in research, I'm --

SPEAKER: But what about the question? Defining the question.

DR. VICKERS: Defining the question. Well okay, defining the question requires some knowledge, right, of what your opportunities are. The questions in large, expensive phase III trials, for example, have to involve consumers importantly.

But what I was saying is that I think also, researchers need the freedom at some early, very preclinical levels, when you're looking at some of the basic sciences. I'm saying perhaps they need the freedom to actually really ignore the demand of the public and the consumers, and develop their own research agendas at the early stage.

Then, we're talking about stages that do not involve patients. This is research that doesn't involve patients in important ways. I think that just comes back to what I'm saying about the difficulty, we don't know how to involve consumers.

I think we don't also know. When not to involve consumers and I say that as a supporter. In every phase III trial I've been involved in we have involved consumers importantly.

DR. SAGAR: We'll give alex the last 30 seconds and then we have to end.

DR. JADAD: I think if consumers were participating meaningfully we would be doing much purer trials than we are doing now. Second: Big issue for you guys. How many of you are from the US? From Canada? From outside the US and Canada? Okay, one. Fifty percent of adults in North America are functionally illiterate when it comes down to health information. There are several studies documenting that. So when 50 percent of the population cannot understand information that goes beyond the label on a medicine bottle, talking about consumer participation is extremely tricky. I think to have adequate consumer participation we need to be involved in them as well, because they happen to be the people need most of the results of the studies that we are trying to refine.

DR. SAGAR: I want to thank our speakers. This was a terrific session. Thank the audience for participating and have a good evening.

(Whereupon, the proceedings were adjourned.)

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