Zan Fleming (00:02:43):
Yeah, well there certainly is. Well, we're just about now ready for Thomas and me to go into a dialogue and it won't be a problem if you jump in, but why don't we get started Thomas? And I'll say that here we're again with another powerhouse session, an installment of the Targeting Healthy Longevity Conference.

Thomas Seoh (00:03:16):
Right. Well, this takes us well over 150 sessions that the conference has generated since our inaugural meeting in London in 2017. The recordings of these sessions are on our YouTube channel. They form an invaluable resource. They can be accessed through the cata.org website.

Zan Fleming (00:03:37):
Right. Our last session when loneliness was not only highly informative, compelling, and even poignant, and it involves a topic that really is important to all of us. Loneliness is an important permanent of health and disease and a major public health challenge. And so we got another installment on loneliness that was our third installment since 2000 or when we did our first topics in London in 2017.

Thomas Seoh (00:04:19):
And before that, that was session three. Session two was an amazing session moderated by George Denberg of the US against Alzheimer's organization and the Davos Alzheimer's Collaborative. It was a panel of global leaders on preempting chronic diseases. One of the memorable exchanges was the CEO of Eli Lilly offering to work together with the heads of the UK MHRA, their FDA and their nice sort of their CMS on making the UK the first obesity free country. So that was kind of fun.

Zan Fleming (00:04:59):
That was fun. And wow, what a conference or session then we had back in May FDA Commissioner Rob Taylor one his first comments to our knowledge on the subject of regulating health span products. And by the way, we expect to have the newly appointed NIH director, Monica to Noli with her former Harvard classmate, cardiologist, Dr. Peter Libby in the new year, talking about their shared interest and preventing both cancer and cardiovascular disease by targeting their shared root causes.

Thomas Seoh (00:05:51):
I think there we're in the act of signing out 2024, we have other sessions that will be announced. Should also mention that in the preparation for this session, we had so much material, so much interesting topics that we are trying to schedule a part two for hopefully for next month. So we'll have more information about that. All the registers will receive information about that as well.

Zan Fleming (00:06:19):
Yeah, do stay tuned for that. This will allow us to drill down further into the effects or the impact of OLS on cognitive function and a number of lessons learned from the sub trials of the main OSMOS trial. So that promises to be another great opportunity to milk the fruits of the Osmos program.

Thomas Seoh (00:06:51):
When we start the chat, I'll be encouraging folks to seed it by saying hello and saying where they're from just for amongst us. Although the house is open and I see people are out there in the audience. I'm speaking to you from a northern Virginia suburb of Washington DC Z. Maybe you could mention and we could have each of our panelists state where they're logged in from.

Zan Fleming (00:07:16):
Yeah, that's actually a good idea. So starting with our most easterly analyst, Aedin Cassidy

Catherine Kwik-Uribe (00:07:28):
And logged

Aedin Cassidy (00:07:28):
In from Belfast in Northern Ireland

Zan Fleming (00:07:32):
And then coming across, I think it would be Scott or no, lowered up in Boston.

Howard Sesso (00:07:41):
Yeah, depending on how you look at the map I suppose. But yeah, no, I'm logging in here from Boston, Massachusetts in the United States. Hi everybody.

Zan Fleming (00:07:49):
And I think Scott is just a little east of Laura. So Scott, go ahead.

Scott Small (00:07:55):
Yeah. Hello, I'm Scott Small from Columbia University New York.

Zan Fleming (00:08:01):
And then Laura, go ahead. You may be west of Catherine, but

Laura Baker (00:08:08):
Hi, I am Laura Baker from Wake Forest University School of Medicine in Winston-Salem, North Carolina

Zan Fleming (00:08:16):
And then to Catherine.

Catherine Kwik-Uribe (00:08:18):
Hi everyone. Catherine Uribe from Everwell Health. I'm calling in from Maryland,

Zan Fleming (00:08:25):
Which is near where I'm and John Erdman over in the Urbana area.

John Erdman (00:08:35):
Right. I'm at the University of Illinois urban banner of champagne in the central part of the country.

Zan Fleming (00:08:43):
Well, very good. We're delighted to have this international panel and it should not be more qualified to talk about the subject of hand. We'll get to it a minute. We are at the top of the hour and we're going to take a few more minutes before we actually start the panel. And so I'm here with Thomas, sir, who is the executive vice president of the institute.

Thomas Seoh (00:09:15):
Well, Z is the president and founder of the ALS Institute and z. What shall we keep talking about?

Zan Fleming (00:09:27):
Well, I think we could say that we have really been looking forward to this session. It's the largest outcome study that you have never heard of, most people have never heard of. And we're going to get into why in just a moment.

Thomas Seoh (00:09:50):
It is a unicorn in the field of large randomized controlled trials among other things because it's studied people in the pre disease state, a stage that we're very interested in at the CATA Institute.

Zan Fleming (00:10:04):
And that is our focus and that is really one of the key points we want to leave with the audience today. Pretty vascular outcome trials are almost a dime a dozen in my field of diabetes and obesity. The public often reads about the results of these trials and there is common as a lot of things we read about in the field, but outcome studies of people without disease for which we want to prevent the disease are dauntingly more difficult to design. And so that's why we're particularly interested in cosmos A trial that is actually studying people who don't yet have the disease or much of it and we're attempting to detect or cosmos attempted to detect a difference in cardiovascular outcomes and that's extremely challenging during the low event rates in another healthy population. And such trials are even more unusual when non-drug intervention is involved because there are far less commercial incentives for products that don't carry the patent protectant and exclusivity provisions of drug.

Thomas Seoh (00:11:43):
And we'll be talking about that unicorn today.

Zan Fleming (00:11:47):
Indeed, while Cosmos studied one flavonol and a multivitamin, and we'll want to emphasize both these agents with cardiovascular and brain health results reported so far and publications on honor that comes expected over the coming years. This SMAs really teaches us much about how and why to obtain evidence for disease prevention or preemption and really is part of the focus of the CATA Institute hoping to develop ways that will accelerate the availability of products that can help not just to treat disease but prevent disease and age-related disability.

Thomas Seoh (00:12:44):
So let's get started. Welcome everyone to targeting Healthy Longevity 2023. Session four, the Cosmos Trials, large randomized controlled trials supporting supplements for healthy longevity. A housekeeping reminder to enter any questions for the speakers in the q and a function of our Zoom webinar platform. We will try to get to as many of them as time allows. As a side note, we were very gratified to receive well over a hundred questions with the registrations. Also, we've just enabled the chat function for audience interaction and just for warmup, for those of you who are willing, please say hi in chat, your affiliation if desired and from where you're logged in. As usual, a recording of this session will be posted to YouTube within a day or so with the link sent to all the registrants. So back to you.

Zan Fleming (00:13:39):
Thanks Thomas. So we are here to talk about the field of flavonols and related nutrients. We want to talk about the scientific basis for the Cosmos trial, give you the background for the plausibility being served in the COSMOS trial. And of course we want to provide some of the key results and learnings of this trial and the subs that run from it. We're going to have our panelists each speak sequentially during this first hour. We may take been part of the hour to get through all six of our panelists, but we will have a lot of time in the second session for a very interactive change and questions from the audience. And I wish we could squeeze more questions and it will be possible to do so. A lot of great questions came in. So let's go to Adine Cassidy. She's professor at the Institute for Global Security at Queen's University in Belfast. She's an expert in the field of nutritional research with a focus on flavanols and related nutrients. Dean, you can start us off by providing a broad summary of the field over the past 20 years and help us put cosmos in the wider

context of research in the field of flavonol and polyphenol research. And you might tell us what led to your interest.

Aedin Cassidy (00:15:28):
Sure, thank you Z and hello everyone. So let me give you the broadest perspective really on flavonoids and flavonoids are the large class of compounds of which the flavonols that we're talking about in cosmos are one of the classes. But I've actually worked in flavonoid research all of my career about 30 years now, even as a PhD student. And way back then the field was in its infancy. But over that time there's been a very steady building of the evidence base for the potential importance of flavonoids for health. And this stems from lab-based studies looking at potential mechanisms of action through to population-based studies and clinical trials, randomized control trials. And actually the best evidence in nutrition is a combination of understanding from mechanisms through to large population-based studies and then really understanding more from the randomized control trials. So that is the best evidence that we have as an integration of that and the needle going in the same direction for all of those.

(00:16:32):
So flavonoids are really interesting bioactive constituents that are in many of the plant-based foods that we consume like tea, like chocolate berries and red wine. And they've been shown in animal models and in lab experiments to have effects on inflammation, improved markers of heart health like lipid levels. But my work has really focused on the health in humans end conducting clinical trials and working with large population-based studies across the world to really understand how do these compounds work in humans and what intakes might we need to actually see some benefits to health. And most of my research is really focused on that cardiometabolic health end. So really interest in heart health and also risk of type two diabetes. So if you think of flavonoids, there are hundreds of them, in fact even a thousand in plants and there are lots of different classes, but the one that we're focusing on today are the flavonols, which are actually sometimes called the Flavin three olds.

(00:17:37):
So a little bit of confusion in terms of the literature there and working with some colleagues at Tufts in Boston. We work to try and summarize all of the high quality data that was available in the literature. Basically conducted a MET analysis of both the population-based studies and the randomized control trials. We pulled all of that data and then you have a lot of power to actually really see what are the potential health benefits. We pulled data from 15 population-based studies and we showed that a higher habitual intake of these flavin oils was associated with a 19% reduction in risk of having a heart attack compared to those who consumed very little of these compounds. So that was the epidemiology or population-based studies. We also pulled all the results from the high quality randomized control trials on flavanols and there were 156 trials to pull, so quite a large amount of data.

(00:18:36):
And we showed that there were significant improvements of biomarkers of heart health and glucose control. So for example, we showed improvements in a measure called flow mediated dilatation, which is actually the goal standard for measuring endothelial function or blood flow, which showed improvements in blood pressure and improvements in HDL and total cholesterol and measures of glucose control. So high flavonoids do result in improvements and what's important in nutrition across a whole myriad of pathways. So it wasn't just an effect on blood flow, but it was also blood pressure, lipids, glucose, and actually the magnitude of improvements that we saw when these data were clinically significant and actually potentially could translate into a significant reduction in future cardiovascular events. And the other important thing is that they're achievable through very small achievable changes to the habitual diet. This isn't some miraculous change to the diet that's needed.

(00:19:42):
So one of the tasks that you asked me, Z was to put cosmos into perspective. So I'll kind of wrap up by doing that. So our comprehensive review essentially highlighted that the majority of the clinical research in flavonoids conducted by that time, this was about 2019, were a very short duration of the 156 trials that we had pulled in there. One, which was my own group, was a year long and all of the others ranged from three week duration to six months. So of course inevitably, because these are short-term trials, all we can look at is surrogate markers of risk of having a heart attack. So that's blood pressure, it's FMD and cholesterol. And although these are really important, what we really needed and what we identified at that point is we really need longer trials that are actually looking at events, looking at heart attacks, looking at strokes, and actually cosmos is the first trial that really set off to fill that critical gap in the literature.

Zan Fleming (00:20:47):
Wow, perfect. Nadine, right on topic and on time. So thank you very much. That brings us now to Dr. Catherine Quick who is now scientific vice president for scientific and regulatory affairs at everwell Health. But he goes back to early days at Mars in their program involving biomedical research of flavanols and was instrumental in the design and the conduct of trial. So Catherine, you had a leading scientific role at Mars and could you start by telling us how Mars got interested in flavanols, what kind of studies of flavanols were done by Mars and how did the company end up supporting Cosmos?

Catherine Kwik-Uribe (00:21:49):
Happy to do so, thank you Z. So I'll start by COSMOS stands for the Cocoa Supplement and Multivitamin outcome study. So my part today is it is to give a little background in terms of the cocoa part. When I worked at Mars was very much involved in the cocoa science program. Many of you may be surprised to learn that really Mars has been investigating cocoa for a really long time. Some of the original publications, actually some of the original work on cocoa actually began in the late nineties with some of the first publications in the field in 1999. Those were largely structured around analytics and it was because at the time ours was really interested in what drives some of the flavor components in cocoa and along the way had to develop analytical technologies to support characterization from that very tangential start. What it led to was the ability to actually really characterize components in cocoa and very similar foods, whether it's apples, sorghum, pears and berries because it led to development of analytics and flavonols and when their chains, they're called pro anthocyanins or procyanidins.

(00:23:02):
This was important because it was a partnership at that time with the USDA, which actually helped develop some of the first databases that began to allow the exploration and the link between diet and health. What it also enabled was then the ability to isolate and characterize these individual components and begin of course as many scientists do doing in vitro work, but it also led the way to the development of actually clinical test materials. When you do clinical studies, we need, especially in the area of nutrition, it can be quite challenging if you start with a food because of just natural variability that exists. So in order to get into being able to do clinical trials, it was important to be able to first develop standardized and highly characterized materials. And that allowed us to be able to then start seeding some human studies. And as Adine talked about these really short-term studies at that time, they might've gone on from one to three days really looking at what was going on from a nitric oxide perspective or what was going on from a vascular function perspective.

(00:24:07):
But what the signals were telling us was that there was an evidence that the flavonol components in cocoa were important or were driving some vascular effects. And so we continued on that road, but we also began to recognize that there was a specific component in cocoa, a molecule called minus epi cagan, which may be in particular very important and we'll probably bring this up a little bit later as we have these conversations

that this is a very potent biomolecule we identified in 2006 using the hill criteria. That actually is one of the key bioactive components in this broad mixture that is cocoa. And then we have the opportunity to actually engage in flavi a grant, a Penn European grant, which allowed us to actually go now even a step further with amazing collaborators across the globe to really look at such things as absorption and metabolism, to really understand the link between what people were eating and health outcomes to get important safety data.

(00:25:09):
And at that time really do some larger trials. Now we're getting into the numbers of 50 and a hundred people for a month's time and beginning to see once again this consistency of these signals all pointing in the same direction of these important cardiovascular benefits, seeing improvements in endothelial function, seeing improvements in cholesterol, seeing improvements in blood pressure. So really sort of once again, getting the reinforcing data to say that there's something going on here. And once again, then there was this, again, this investment in analytics to really understand metabolism and what you eat isn't necessarily what appears in the bloodstream and putting the connection together. So then we could also then develop biomarkers of intake. And once again, as other panel members begin to talk about the research, not only knowing what people are eating, either their intervention, but from background diet and then the relationship to the health outcomes, being able to have these biomarkers of intake has become really important.

(00:26:10):
And that was another outcome of this pretty amazing research program. So we're having a consistency of data across time that is pointing to the benefits of Coco Flavanols and flavonols in general on cardiovascular outcomes. We're also beginning to explore the benefits on cognition. Some of the original papers, taking a very broad view, doing a variety of cognitive tasks over a period of four to 12 weeks and seeing improvements. And then beginning to work with Dr. Scott Small who'll talk a little bit later on, really honing in on cognition and actually very specifically memory and seeing these improvements in hippocampal dependent memory. And so all of this work is going on and is being published and is really once again reinforcing the benefits of flavanols from, in this case cocoa. But we're also seeing it appear in literature flavanols from other foods also having cardiovascular effects. And so while most of the panel today we really will talk about cosmos, cosmos is isn't the entry point into the conversation around Flavonols?

(00:27:22):
It's actually a milestone and a long journey of 20, 30 years of research on these compounds by Mars and by others really setting the stage to say and really answer key questions with cosmos. I mean fundamentally are flavonols good for you? Do Flavonols have the ability to actually tackle one of the main diseases across the globe today, which is cardiovascular disease? Can flavonols included in the diet, have effects in preventing and or even treating cardiovascular disease? And so that really gets us to the starting point of all this previous work by us and by others really set the stage to really begin to now actually entertain a conversation to say, are we ready to go to the next step? While Mars was thinking about these things, we actually happened to get a phone call of another party interested in saying, would we be willing to consider and collaborate and help on a study called Cosmos? And perhaps with that, I'll turn that over. Back to you Suzanne, and likely Howard.

Zan Fleming (00:28:28):
Wow, that was such a great setup for Howard. Dr. Howard Saysso, who is the associate professor in the division of preventive medicine at Harvard Medical School and co-lead investigator of the Cosmos trial. Now Howard, you bring a career long interest in epidemiology and prevention of cardiovascular disease and cancer. You're ideal for describing the key points of the main trials, origin and rationale. And you can tell us what interested you start you and co-PI, Dr. Joanne Manson in Flavanols and what then led to the

conceptualization execution of cosms. You might even fill in some of the key outcomes of Cosmos and talk about the sub trials that evolve from the main program.

Howard Sesso (00:29:30):
Thanks Anne, and thanks Catherine and Adine for the intros into this. I think first and foremost, Joanna Manson, my co-PI on the Cosmos trial sends or regrets. She had a conflict at this time, but more to the point I think as everyone's already started to point out, this is always a much longer journey than people appreciate. The trial is in many ways it's not meant to be the final test either when we're testing these types of interventions, but it's usually a combination of a lot of data that have come into it. As Adine points out, there was a lot of strong observational evidence, not just for the cocoa extract or flavanol intervention, but there was also building evidence for the other part of Cosmos, the multivitamin intervention as well with potential benefits on cancer from a previous large scale long-term trial that Joanne and I and others in our division of preventive medicine had done called the Physician's Health Study two.

(00:30:23):
But one thing that's really critical to this and thinking about how Cosmos got conceptualized, that is probably one of the most important messages from my perspective, is that this type of research can't be done without having it be multimodal in terms of who's conceiving it. It's not that it can't be done by us in academia, it's not that it can't be done separately in industry. It's not that it can't be done perhaps in a government or other foundational level, but the best work that usually comes out of, especially in nutrition research and aging research and healthy aging is usually that research that brings everyone together to the table to collaborate and put the best foot forward in terms of the science. And in many ways, cosmos reflects all of that. When we had first reached out to Mars with their potential interest in supporting Cosmos, we don't know what to expect, right?

(00:31:16):
In a lot of ways it's a bit of a risk because the way that dietary supplements and foods are overseen, you don't really have to have the same thresholds of evidence that you might for say an anti-hypertensive. So in a certain level there's a lot to lose as much as there is a lot to gain. But at the same time, there was such a strong buildup of evidence from the observational studies as well as from shorter term clinical trials supporting coco flavanols for cardiovascular disease as well as potentially for the multivitamin looking at cancer outcomes. And so from all of that, cosmos was born. One thing that our group here in Boston is pretty good at over the years is doing these very large scale nationally representative trials that are focused on primary prevention back to what Zion was getting at before, which is that it's one thing to focus on a specific target audience or population.

(00:32:15):
It's another thing to really start much earlier in the prevention process. It's one thing to say you've developed cardiovascular disease, how can we treat it better? Lots of ways to do that. But more important is what can we do to prevent it? And especially in the context of healthy aging. And so when we were designing the cocoa supplement and the multivitamin outcome study or cosmos, this was ultimately a study that included almost 21 and 5,000 older US men and women. So these were men aged 60 and up, women aged 65 and up that were free of baseline cardiovascular disease as well as recently diagnosed cancer. In fact, we had about 3,500 participants that enrolled into Cosmos that reported a previous history of cancer. So they were randomized into a trial where we tested a cocoa extract intervention and building a little bit on what Catherine was alluding to, it's always a little challenging even designing the intervention to be perfectly honest, because what we ultimately tested in cosmos was the cocoa extract in supplemental form versus a placebo.

(00:33:19):

But you can make very similar arguments as to whether or not you should be testing specific components of cocoa extract that we think might be driving the effects. So whether it might be the Coco Flavanols or maybe it's the minus epi catechin or other components that are in the cocoa bean. Even that decision when we were designing cosmos is kind of wrought with challenges. Are we testing it as a bioactive food or are we testing the specific bioactive components? Nevertheless, when we conducted Cosmos, these types of trials do take time, and that's the other challenge of these, you design them because they're primary prevention for the most part. And if we're going to wait for enough people to develop the outcomes of interest such as cardiovascular disease, cancer, and also doing repeated cognitive assessments and other types of assessments, you need the power of time and patience, for lack of a better word.

(00:34:14):
So for the 21 and a half thousand or so participants from Cosmos who came in, they were asked to be taking these pills randomly allocated for a median of about three and a half years of follow-up some a little bit longer, some a little bit less. And it's actually nice to see in the chat that we have a former Cosmos participant listening in. These participants are as much collaborators on the study from our perspective as those that are supporting it. And Cosmos, it should be noted, was supported not just through generous support from Mars Edge, but also through the support of the NIH through different grants that we'd received, as well as ancillary study grants that you'll hear about. And also from Pfizer consumer healthcare ion who was producing the other intervention, the multivitamin that we were testing. But that being said, just to give you a sense of the Cosmos eligibility criteria, again, these were older men and women, no history of cardiovascular disease.

(00:35:10):
They were all willing to forego taking a multivitamin, taking a cocoa extract supplement. Our primary outcomes were focused around incident cardiovascular disease as well as incident cancer that developed during follow-up. We had a number of other aims that we built in on the basis of all of the wealth of data that we also collected over time. This included bloods that were collected for biomarker assessments, cognitive assessments that we hear more about, and just regular surveys that would go out every six months asking about pretty much anything that's been happening over the last period of time. But to give you just a sense of the scope of this, we had to ultimately enroll nearly about 3 million. We had to reach out to about 3 million people around the United States to enroll the 22,000 or so participants. So it just takes a lot of time and energy and wherewithal to give you a sense of the results very briefly as we dive into it.

(00:36:09):
So for the cocoa extract or Coco Flavanol intervention, our primary outcome again was total cardiovascular events. Over the course of the three and a half years in these 21 and a half thousand people, we had about 850, 860 or so total events that we had to wait for to develop and confirm. And based on that, when we did two different sets of analyses, the first set of analyses that we did are what we call intention to treat analyses once randomized, always analyzed. So regardless of what you do once you start taking the pills, we're going to treat you as if that's what you're still taking. And those results, what we found overall was that there was a 10% reduction in total cardiovascular events for those taking the cocoa extract versus placebo. This did not reach statistical significance. However, we did note that there was a 27% reduction in cardiovascular disease death that was statistically significant.

(00:37:06):
We also conducted similar analyses that are what we call compliance-based or per protocol analysis where instead of just saying once randomized always analyzed, instead, if I decide after two or three years, I'm a little tired of being a participant, I'm tired of taking the pills or maybe I have other reasons that I might decide to stop, we're only analyzing the data for the time that you actually took the pills. When we looked at those results, we actually found that the effects strengthened for the cocoa extract intervention on total

cardiovascular events and became statistically significant. It became a 15% reduction in total cardiovascular disease, and those results for cardiovascular disease death also strengthened.

(00:37:48):
It should also be noted briefly that we had a biomarker of compliance gamma Valero lactone metabolite that we also were able to measure, and we saw quite clearly that those that were taking the cocoa extract saw about a threefold increase in this more objective biomarker of compliance. And we're still looking to see how this might relate to total cardiovascular disease events in cosmos. And then one final note, and until I pass it along is that we also looked at the multivitamin in the context of invasive cancer. This is based on previous results that we had seen in another long-term trial that we had done the physician's health study too, where we saw a significant reduction in cancer risk, but we were unable to reproduce those findings in cosmos. There was no of the multivitamin on the primary outcome of total invasive cancer. One final bit is that cosmos is a unique trial in that it's a hybrid clinical trial.

(00:38:47):
And what I mean by that is that we're not just focused on these primary outcomes and findings that we're discussing briefly now for cardiovascular disease, cancer cognition and other aspects of healthy aging. But we collect data in a way that we can look at the mechanisms of effect in combination with the longer term clinical events that we also seek to prevent. So what we have is an opportunity to look at not just the broader strokes, but understand the mechanisms of effect that we can learn from cosmos and hope to apply that into other areas of nutrition research and aging research as well. So with that, I'd like to turn attention next to Dr. Scott Small, who was the lead of one of the key cognitive studies that we had in Cosmos.

Zan Fleming (00:39:31):
Excellent, Howard, thank you so much. And we are now to Dr. Scott Small who's professor of neurology at Columbia University and lead investigator of the Cosmos Web sub trial. Scott will explain that in a moment. Scott is a clinical neurologist and a neuroscientist with a focus on Alzheimer's disease and normal cognitive aging. So we turned to Scott for a key finding of the Cosmos web study that dietary flavanol here to restore the camp dependent memory in older adults who have low flavonol consumption. So to me, that is an astounding observation in itself, but there is a lot more that comes out of this particular substudy. So Scott, start with what led to your interest in flavanols and involvement in flavanol research and then get into the substudy.

Scott Small (00:40:37):
Yes, of course. Thank you, Z. Hello everyone. And yeah, I think the history here for me in particular is relevant. As Zan said, I'm a neurologist neuroscientist who's interested in age-related memory decline, particularly that emanates from the hippocampus, a structure in the brain critical for memory, and there really are two conditions to consider. One is the early stages of Alzheimer's, which starts in the hippocampus before it progresses in its death march across the cortex. But then there's also something called cognitive aging, which is equivalent to presbyopia of the brain. I have presbyopia, I don't have an eye disease, I have the normal wear and tear of my eyes. That's also happening in all of our hippocampus as we age. And in the beginning of our research program, we showed that different parts of the hippocampus are linked to Alzheimer's on the one hand and cognitive aging on the other.

(00:41:44):
And that was from observational studies in humans and various animal models using high resolution imaging techniques. But we wanted to really confirm that mechanistically. And at that point we started collaborating with Rusty Gage from the Salk Institute, who actually an interesting collaboration sponsored in part by DARPA to work together with Mars. Rusty and myself and Rusty made the really interesting observation that flavanols, when fed to mice will improve the function of the part of the hippocampus.

That's the seat of cognitive aging. Names don't matter, but if they do, it's called the dent, HIS. So that was really interesting. And then we began to work with Mars to do clinical trials, basically to confirm the hypothesis that the dent h iris is the seat of cognitive aging. And this has led to three trials in greater sophistication, one in nature neuroscience 2014 one in science report 2021.

(00:42:59):
And the really most informative study that really changed our views on things was the cosmos web, and it was called Cosmos Web. It's an ancillary of the incredible study that Joanne and Howie have put together because my collaborator at Columbia, Adam Brickman was able to translate cognitive tests that are usually done in a neuropsychological, neuropsychologist neuropsychologist's office into a home-based web-based computer-based tool that he then validated. The reason the way things shifted in a really interesting way, we had initially thought from our earlier studies that the flavanols are sort of like supplements or to use an old fashioned term neurotropics. They boost up the function of the dent h rs. But in this latest study, because of what Catherine was telling you, they had developed this really incredible biomarker of habitual flavonol consumption, a urine based biomarker. And so the upshot of Cosmo's web is that if you're relatively deficient in your habitual consumption, and I have to be careful by saying relative, because deficiency could be a clinical term, you're more likely to have poor hippocampal dependent memory.

(00:44:22):
And then if you are in that relative deficient subgroup, and then over a few years you consume flavanols, your hippocampal dependent memory normalizes to those in the high flavonol group. And so now we're not quite there yet, but we're getting to the point to argue that flavonols, these particular form of flavonols are potential ideological drivers of age-related memory decline. Remember we first got into this to try to shore up the hypothesis, but now using the logic of depletion repletion, we're getting close to the point of saying that maybe flavanol, if you don't consume enough flavanols, if you're microbiome doesn't allow you to take up enough, even if you consume them, that might be one cause. And I use the causal word carefully of age-related, hippocampal based cognitive aging. So that to us was very fascinating. And of course, we need to replicate this in a number of subsequent studies. So I think that's really the upshot. Z, unless you want me to go into some more details,

Zan Fleming (00:45:37):
Maybe you could refresh or give a summary of how the sub trials were done. In other words, they were also subjects in the main trial, but what was the logistics and the sort of procedure used to peel off these substudies?

Scott Small (00:46:00):
Yeah, and here Howard can also step in. This was an incredible collaboration. I think what Howard said is right, it really takes a village. We didn't get to study the 21,000 participants in the parent company, but we were able to study nearly 3000 subjects who were willing to participate in the ancillary, who were willing to have cognitive tests, tests. And so I think it's a great example of a collaboration across universities in this case.

Howard Sesso (00:46:34):
Just to build very briefly on Scott's comment, I mean one of the fun things honestly of conducting the trial is the ability to collaborate, not just with Scott and his colleagues at Columbia, but also with Laura Baker who will be speaking shortly and her colleagues at Wake Forest. But when the participants are enrolled into the study, we basically, as they're enrolling in, we say, of course we're trying to get you into the main trial, but would you be interested in doing other things? And so it's a blood collection if you happen to be in the Boston area, might you want to come in for in-person clinical assessments for even deeper phenotyping to understand more about the mechanisms of healthy aging. Then this other piece is of course the cognitive

assessments. We basically say, would you be interested in doing some cognitive assessments? You have to think a little bit more carefully about who says yes and no to that. Of course, there's this volunteer effect, but we had these older adults, their credit were technologically adept and said, I'm curious to try these web-based assessments for the Cosmos web study. And it's also a nice foray into Laura Baker who will now jump into some of the descriptions of the Cosmos mind study, which was not computer-based, but rather telephone-based to compliment the web-based assessments to look at cognition in different ways.

Zan Fleming (00:47:51):
Right. Well, terrific, John, and very helpful Howard to bring us to Laura, who is professor of gerontology and geriatric medicine at Wake Forest University School of Medicine. She is a neuroscientist, an epidemiologist with an interest in the study of Alzheimer's and other age related diseases. Laura, describe how you became interested in the impact of flavonols on dementia and your involvement in the Cosmos Mind study. This is yet another substudy of the main Cosmos trial and the design and results of Cosmos mind.

Laura Baker (00:48:38):
Happy to do that and welcome everyone. I think I'll start off by saying how did we come to the table? I think we, as Howie said, we partner beyond Cosmos on many other studies. We share and work with each other on Cosmos is one example, but many of us work together on many other trials and Howie and his team and our team have worked together for years on the Women's Health Initiative. And so it was just a natural that they're doing this fantastic study in over 20,000 people. Our expertise at Wake Forest is cognitive assessments, and in particular because of our work with Women's Health Initiative, cognitive assessments conducted over the phone, which really, it sounds pretty straightforward, but what we feel is important about that approach is that you have access to people who can't come to a clinic who live far away from a clinic who maybe don't want, don't trust a clinic, but they will talk to us on the phone.

(00:49:43):
So I feel like it's an important strategy to reach out into underserved neighborhoods and regions. That's why we were just very grateful for the opportunity to partner with Howie and Joanne on this particular study. So we are, as Scott talked about a moment ago, we were an ancillary study to the main Cosmos trial, meaning we recruited our participants directly from the main trial. What was a little different about what we did, we really wanted to make sure we could capture as much diversity in our enrollment as possible in terms of mostly race, ethnicity, education. So when we had all these folks saying, yes, we'll participate in Cosmos Mine, we had of course a very long queue of people to get to. We enrolled over 2000 people in Cosmos Mine, but we prioritized folks who were from underserved areas and those folks went to the front of the line and as a result, we were able to increase our representation a little bit more to the best of our ability within the trial.

(00:50:54):
So I think if I were just to add on to what you were asking a moment ago, Z, there are ways to recruit from a main trial. There are ways to, and I think what was special about ours is we were able to reach in areas we really covered in Cosmos mind. We were reaching out all over the country and we were in rural areas, we were in urban areas. I think we just did a good job at finding folks who could not come to a clinic. So let me just go from there and just kind of tell you a little bit about the study. So we were very interested in looking at the cocal flavonols in particular effects on cognition. That's what's got our attention initially for all the reasons that you've heard today, just the potential impact of Coco Flavonols on cardiovascular events.

(00:51:45):
And I'm a cognitive scientist, and so I've been studying for years the effects of cardiovascular disease on cognitive function and cognitive decline in older adults. So of course, we're very interested in learning whether coco extract that was administered in the Cosmos trial might protect individuals from cognitive

decline. Now, we understood that we had some limitations. We're only going to watch these folks for three years, and if you start off with healthy individuals, they don't decline. It takes a little bit longer for them to decline. But so our main focus then was on cognitive trajectory, not incident cognitive impairment having to do with mild cognitive impairment or Alzheimer's disease, but really cognitive trajectory. So that was our focus. We were interested in the cocal flavonols of course, but also the multivitamins. There were still some unanswered questions in the field about whether multivitamins might add protection for cognitive health for older adults, and it might improved your trajectory over time. The main study, I think Howie had mentioned this, I just made reference to it a moment ago, that one of the largest studies that's ever been conducted in multivitamin world is the physician's health study too, where they watched older male physicians that a follow-up period was very long. They did take, they were, was it randomized controlled trial where they received multivitamin or placebo and they administered these telephone cognitive assessments. Over time, our batteries are a little bit different. I think our tests are a little bit more difficult.

(00:53:25):
The things that we ask people to remember are much greater in volume, for example, than what was asked of the physicians and the physicians health study. Again, only male physicians, they found no benefit in cognition, but we felt like there's still many unanswered questions there. We felt like it was important for us to embark on this more rigorous, not more rigorous, but another rigorous assessment of cognition. So we were very excited about testing both of those. Our goal was to look at change in cognition over time. We used a measure that we feel very strongly that we should be using as a standard across the field whenever we're looking at cognitive change, and that is a global composite score. I see a lot of, when you look through the literature and you'll see whatever it is that you're looking at in terms of cognition, you may see this performance on this single test improved, whereas a performance on this test did not.

(00:54:25):
And that's very confusing for us as scientists, but it is also more confusing, I think, for the public. And so as a cognitive scientist myself, I'm of the mindset that if I can create, if we as a team with not just my ideas, but group ideas that gathered from experts, if we can develop a composite that accurately captures all the abilities we're trying to watch. So in this case, we were looking at memory and executive function. If we can capture one composite score and include different tests, and if we can see change on that composite score, we think we really have something. If we, we administer 10 different tests and get change on one test, but not another, what's our message? So we're really strong advocates of these composite scores. So what we did is we enrolled these folks. They were agreed to participate in a three-year assessments.

(00:55:26):
So baseline and annually for these cognitive assessments. These assessments took about 45 minutes to an hour on the phone, depending on the person we tested, really focused on memory and executive function so we could create these composite scores. We worked with the Cosmos team, so we would always ask, are you taking your supplements? And if not, we would contact them. We'd be back and forth just to really truly team spirit to try to get our participants trying to stay with the program as much as possible. So what happened is we ended up recruiting, well, lemme just say about our enrollment criteria first. We were basically in line with Cosmos. The only thing, we had a few different, just a couple of different criteria. We only included people who were 65 and older. Cosmos was 60 and older. We felt like if we had only three years to watch these folks, we really need to find people who are at greater risk for decline.

(00:56:23):
And 60 year olds are really in a different place than 65 year olds. So we restricted the range for age. And if you had a self-reported diagnosis of dementia, we excluded you. The participant burden would be too high if you were on insulin for type two diabetes, we excluded you. There are some papers showing that insulin use, systemic insulin use can have detrimental effects on cognition. We didn't want to work against

ourselves there. So folks completed these tests annually for at baseline. And then once a year, really our participants, they liked for these tests, they would call us and say, Hey, it's time for my test. When are you going to call us? So I think that's a testament to the parent trial did and their relationship that they built with these participants. And then we were able to reinforce those relationships. So this is what we found.

(00:57:18):
Lemme just talk first about the coco, the cocoa extract that was administered in the main trial. Remember, we didn't administer anything different. We just took their participants or had their participants participate in our group for the cocoa extract. We did not see a benefit over time. Over the three years that we watched these individuals, we saw some practice effects retest improvement from baseline to year two, which is pretty common in trials that administer repeat cognitive testing. If you don't get practice effects, I'm more concerned that there's something else going on that practice effects are to be expected. So we saw those practice effects for both groups, but those two, the trajectories of the placebo and the cocoa extract group did not pull away from each other statistically right on top of each other. So we were really disappointed. That's where we really expected to see the difference and we did not see it.

(00:58:19):
It's possible I'm not going to return to talking about this anymore, so I just wanted to say it's possible we hadn't watched 'em long enough. It's possible it takes longer than a three year period to see it. It's also possible that our tests were not sensitive enough. I mean, all of ours are administered over the phone. There's only so much we can do in terms of sensitivity. I think Scott and Adam Rickman's test, when they use the computer, we can get trial by trial reaction time when they finished digging and doing a little bit more work, trying to figure out who is the responder and who's not. We're going to learn a lot more there, but we're limited. So it's possible that our tests were more of a blunt instrument, so to speak. So I am going to talk now just for a moment about the multivitamin.

(00:59:03):
That was the other part of this study. We, in contrast to what we saw in cocoa extract, we did see a benefit. We saw the same practice retest effect from baseline to year two. Same thing. I remember, these are the same people, but those lines, those trajectories that are describing those who were taking the multivitamin versus the matched placebo, they separated and it was a market separation so that there seemed to be some improvement for those who were taking the multivitamin. And we found this to be true for not only the global composite, but also for the components of that global composite. So we had sub composites. So looking just at memory or just at executive function, we saw benefits in both of those. And then the last finding that we had with the multivitamin was, and we're excited about this, it needs to be repeated.

(00:59:57):
We need to make sure that there's a lot of extra work to do, but it's still promising, it's still worth talking about. And that is for those individuals who came into the main trial who reported significant cardiovascular events at baseline, and we're talking about TIAs, congestive heart failure, PTCA stent, those kinds of more significant events, people who reported those at baseline, they seem to show even a more robust benefit to the multivitamin. And we saw at baseline, those who had significant cardiovascular disease were performed lower than those without. But what we did see is those who were taking the multivitamin who had cardiovascular disease, they improved. Whereas those on the placebo showed the stereotypic or classic characteristic decline. The continued decline. We know this in the cognitive assessment world, people with cardiovascular disease, they decline at a faster rate on cognition. We saw that here in our study.

(01:01:00):
We saw that those on the placebo decline, they showed the characteristic decline. Those on multivitamin did not. And actually they actually improved to the level of the individuals who did not report cardiovascular

disease at baseline. So still, that was based on 200 of our 2000 people, only 10% reported these more significant events. So it definitely, we do need to repeat that. I think the last point I'll make is we did people always ask, what does this mean? I mean, you saw benefit, but how much and can you tell a difference? Can I tell a difference by talking to you? And no, we can't answer any of that yet. There's still lots of work to do, and we don't know what the clinical significance is yet. I mean, the effect was small. I think some of the questions I saw was the effect was small. It was like a 0.07 effect size.

(01:01:51):
That's a very small effect. But what I want to say is some of the more recent Alzheimer's prevention pharmacologic strategies are smaller than that, that have been approved by the FDA. So I think in our strategy at trying to find something to slow cognitive aging, we're not about finding the magic bullet, the silver magic bullet. Our goal is to find strategies that add layers of protection against decline. And if we can build one layer on top of another, maybe we will have a magic budget bullet. But we don't have that yet. But our goal was never to find that silver bullet. So the last closing statement I'll make is just based on our, what is our clinical significance? Well, we don't know. But what we were able to do is take a look at the data that we have. Remember we had over 2000 people and we looked at what are your global scores by age?

(01:02:46):
So we had people from 65 to 94, 94 years old. And so we could look at the pattern of when you're 65, here's your cognitive score, and when you're 94, here's your cognitive score. And we could say, for every year that you get older, you lose that much. We could say that by looking at our data. When we combine that with the benefit of the multivitamin, our estimates from our data alone is that the multivitamin in our study appeared to slow cognitive aging by 60% or 1.8 years, not a silver bullet, but it is possible. It could be one layer of protection that could be beneficial added with other types of layers like cardiovascular protection using pharmacologic agents.

Zan Fleming (01:03:31):
Wow. Well, Laura, that is quite a dramatic finding. And we'll come back to Scott Small and a comparable finding in the Comos web in the next session. But let's do go to Don Erdman, who Dr. John Erdman is Professor emeritus of nutrition and food science at the University of Illinois at Urbana. But John is a icon in the nutritional field and will take us up to the big picture, the public health implications of cosmos, and formed by his distinguished research and nutrition on his focus on keratinoid and other bioactives. Now John is actively involved in the process of establishing and updating dietary reference intake. So-called RH or DRI standards. And so flavonols are bioactives but are not yet part of the DRNI like framework. Does evidence from Cosmos and other studies provide a basis for a flavonol RDI? What else is needed? And feel free to touch on any other major points.

John Erdman (01:04:56):
Thanks, van. First, let me give a little background. Many people are familiar with the RDAs recommended dietary allowances, and those were established in the US back in 1941. And why were they established? Because we were heading off to World War II in Europe and our federal government and the president wanted to know what kinds of foods and how much food would be necessary for soldiers who were fighting across the sea. So the first RDA report essentially set out recommended dietary allowances for a number of nutrients for the soldiers. Well, over the years, this evolved into, finally, in the two 1990s and two thousands, with a number of values including the RDAs. And we now call these dietary reference intakes, and they're actually meant for essential nutrients. And essentiality in a nutrition area means that if you remove the nutrient from the diet, say vitamin C, for a long enough time, there'll be a deficiency disease such as scurvy. And if you put the nutrient back in, the scurvy will go away. Well, flattened three alls and other dietary bioactives don't meet the classic essentiality criteria.

(01:06:39):
Now, that said, that doesn't mean that not important in health. In fact, we've heard this morning about how important the flavanol containing supplement has been to reducing the risk of cardiovascular disease and having an impact on cognitive function. So there's a differentiation between a deficiency disease and more optimal health. So many of us would argue that a number of bioactives, including flam three oils or lutein ver macular degeneration are important for health and deserve to have recommendations. Dietary recommendations, the DRI committees have for a long time intended to have a panel just discussing recommendations for bioactive components. This has not happened. I say this has been 20 years. When there's an intent to do it Well, why hasn't that? Well, there's always a more higher priority. So right now the central nutrients are being revised. A number of them have been done, and next up is revised recommendations for carbohydrates, proteins, and fats.

(01:08:08):
So we need to create a more priority for evaluating these non central components. And what that's going to require is authoritative bodies. The Food Nutrition Board, DRIs as one authoritative body. You could look, the American Heart Association could be another authoritative body to make recommendations or the dietetics association. So getting to your question specifically Van, I think the Cosmos trial and the auxiliary trials provide a foundation for making recommendations. In fact, the Academy of Dietetics Nutrition dietetics has already made a recommendation for a specific level for flavonoids. So I look forward to our discussion session coming up.

Scott Small (01:09:15):
Could I just quickly add something that we discussed internally, which I think is interesting? I think the history of the recommendations a hundred and so years ago were really focused on the developing body and brain, and now that we know that the physiology of aging is different, I can easily imagine a different set of recommendations for aging individuals. Would you agree with that, John?

John Erdman (01:09:42):
Absolutely. And in fact, as we've gone along the way with different RDAs, we now have a plus 65 category. We also have it under two categories. Those were not in place before, so I agree with you. Yes.

Zan Fleming (01:10:03):
Well that's a terrific discussion right there and we're going to have more of it when we come back in five minutes. We'll really drill down on some important points, even answer in part the question why haven't you heard much about the Cosmos trial? There's some important reasons for that and then we'll cover a lot of questions that have come up during this session and even questions that were submitted prior to the session. So we're going to take a five minute break. We'll actually make it three and a half minutes and come back right at five minutes after the hour. I hope you had enough time to take a break, but we don't want to lose the opportunity to utilize our panel. And so let's get started. Just to get things rolling, let's do a quick round Robin on the question. From your perspective, what is the most important result or learning of the Cosmos program, both the main trial and the two substudies? So why don't we start again with the dean at be, since it's getting late there, she may still be on Bri, why don't we, let's go to Howard.

Howard Sesso (01:14:17):
Yeah, I mean I can certainly speak to the broader aspects of Cosmos. I think it's interesting, my thoughts, my answer to that question is different now than it was when we were first initiating Cosmos. Quite frankly now almost 10 years ago is really when we were first putting the pieces together to get it started. My answer now I think focuses more on this concept of healthy aging and understanding how, for example, the Coco Flavanols or cocoa extract fit into that context. We know that in the context of healthy aging, certainly cardiovascular disease is certainly a prominent part of that. No different than cancer cognition, frailty and all

the other things that we basically encumber as we get older. So I think I have a much more, I would say broader view of the utility of Cosmos as an important contribution given the fact that Cosmos is actually one of the oldest trials in terms of the age of the participants when they began, our mean age was approximately 72 years of age when the Cosmos participants were first randomized and we're still continuing to follow them up, not just for the trial intervention pieces but as a large scale cohort related around healthy aging.

(01:15:41):
So I think from my perspective, I think there's much broader ramifications of what we can learn from Cosmos including the interventions for the cocoa extract and the multivitamin components, but also just how can we age and live better and more functionally

Zan Fleming (01:15:58):
And adine we're just going around last game, what from your perspective is the most important learning from?

Aedin Cassidy (01:16:09):
Well, I mean I think it's in nutrition. We have a lot of short-term trials and rarely do we have these really important endpoint trials and we're showing that you can shift the needle. It may not have been significant for the primary endpoint, but it was how he looked at compliance measures and that's what we really need particularly to get in a medics to really think about the importance of nutrition because all very well showing small changes in blood pressure and cholesterol, but you really need to see does it actually work in terms of the event. And I think Laura made a really important point earlier too, talking about the layering of protection and I think I'd alluded to that too, that it's just very small changes to the diet can have quite significant clinically relevant benefits, so small changes can really have an impact.

Zan Fleming (01:17:05):
Excellent. Catherine, how about you?

Catherine Kwik-Uribe (01:17:09):
I think as we've talked about, we had a lot of small trials that lead up to this finding. I think there are two components. One is sort of the ability to see these profound effects, particularly in those who are compliant and then the safety. And so you have these two things that tell you there's an effect and actually a pretty profound effect and it was safe and well tolerated and therefore you are in a position to say you can begin to recommend that flavanols should be included in the diet. We as John talked about the a and d recommendation. So I think what's exciting is that particularly because they're safe, there's emerging evidence of their efficacy. And so layering is the phrase may be from this session today, sort of the layering on of protection and things that people can do today, cosmos did use a cocoa extract supplement that was done largely based on the evidence, but also to really provide a very standardized uniform material that could be provided over a window of up to five years. But the reality is people can get flavonols from a variety of foods, and so getting these flavanols from foods is well within reach. And so I think message to take away from here is we should be getting the right macronutrients, the right micronutrients, but also flavanols are probably important to our health now and to healthy aging overall.

Zan Fleming (01:18:44):
Perfect. Let's switch gears a little bit and have Laura and Scott compare and contrast their two sub trials and in fact you see qualitatively the same two primary results and so you might talk about what you saw and what you didn't see why and what would be the next study you would do given what you've learned in these sub trials?

Scott Small (01:19:13):
I'll let you go first, Scott. Okay. To me, and maybe also to extend the previous question, what I've learned the most here, which is what I think the field knows is you need biomarkers. If you have biomarkers, and I think Catherine was talking about the difficulty of diet studies, nutrient studies. John was talking about essential nutrients. If you think back to how those nutrients were determined to be essential is because you had a biomarker quote unquote of different vitamin deficiencies, folate deficiencies, and then you can play the depletion repletion game. And as I now look across multiple type based recommendations, whether it's mine, mediterranean diet, multivitamins, I think it's really, really critical that there be some objective biomarker to know what you're really targeting. And that might very easily explain the small effect sizes because if it's really that subset who's deficient that's gaining it, you're going to dilute out the effect.

(01:20:30):
And so to answer the question with that as a background, one of the things we really would like to do, and we're already gearing up to do that, we did not design this trial to enroll in randomized people who are formally deficient based on the, there is actually a normal distribution of flavanol consumption based on that biomarker that we all talked about 50,000 individuals. So we can actually formally find two standard deviations below the normal and you don't have to go far to find people who have very poor diets formerly deficient in habitual flavanol consumption and then to replete them. Then I think back to the issue of effect size, we also saw a small effect size because our low flavanol consumers were really not on the extreme end of that distribution. And I think that would be required also to shore up the conclusion on causality. Excellent. Laura,

Laura Baker (01:21:41):
If I could speak to Linda, one of the first comments before we started with Scott and I about whether food possibly could provide what we need. A lot of my work is within underserved populations who don't have access to certain foods, they live in food deserts, they don't trust healthcare for many reasons that are well-deserved. And just to say I think we just need to be very mindful of what all people have access to and not everyone has access. So maybe supplements are going to have an important role and that's why the need for more studies, more trials with representative cohorts. So Cosmos was not representative, it was predominantly white and well-educated, that's a function of you. It's a function of our recruitment strategies is a function of how we approach people, how we recruit and who's willing, who has the time maybe to do this.

(01:22:44):
So it's possible that when we get into more diverse, we can engage and develop relationships with more diverse populations and they agree to participate, maybe we're going to find something different and maybe some of our little small signals will be larger in more diverse groups. So that's why it's so important that all not only do the science, but we also spend time connecting with our communities to make sure that they're all represented at the table. Otherwise we don't want any solution for a segment of the population. That's just not our job. In terms of our studies, Scott and Adam did versus what we did, I really liked the compliment. Ours was on the phone, theirs was through a link that you received through email and what we did learn, we did a head-to-head comparison of what our people look like in Cosmos mind and what the people look like in Cosmos Web and Cosmos Web, a little healthier people, they're little bit more, they exercise a little bit more, they have lower cardiovascular disease, they're a little healthier.

(01:23:49):
But that just speaks to the point of how we approach people affects who comes to us and I think, so more studies like this where we all work together to try to find all different kinds of people through innovative ways I think is going to help us. So we have a little bit of a difference in our results, but in terms of specific tests that showed benefit, but I think if you were to combine the two, we both saw cognitive benefit with

the multivitamin. We didn't see it as I said with a cocoa extract, but it may be that our tests were not sensitive enough and his computer tests were in fact more sensitive. So the other thing is we didn't look at prior coco flavonol levels in our participants and then relate to their response to the cocoa extract. We didn't do that. So it's possible that when we continue doing our deep data digging, maybe we'll see something there. So just that the more research is needed and it's not easy just to pump out a quick trial. It takes a lot of effort. So I think people get frustrated that we can't move science along faster, but it really takes people like yourselves in the audience to and those that to say, raise your hand and say I'll participate otherwise we're going to be slow in our discovery for years to come.

Howard Sesso (01:25:11):
Thank you for that. Let's help. Sorry, can I build on that? Go ahead, sorry. No, I think both Laura and Scott, everyone's making some good points here and I think, so point number one is that representation in clinical trials is always a challenge, both as a trialist and of course for all of us trying to interpret these trials. We all do the best that we can, but we still need to do better in terms of targeting a more diverse population, the underrepresented components of the population, those that might be more susceptible to lower intake of Coco flavanols and or essential vitamins and minerals for that matter. The one nice thing about Cosmos I like to highlight is that for both interventions actually we have the ability to have a nice objective biomarker that provides a little bit more gravitas to our results. So again, for the cocoa extract supplement, we have this nice biomarker gamma Valero lactone metabolite GVLM that allows, and we showed quite clearly in our main trial results that it tracks nicely with compliance and with those that were getting the intervention versus those that were not.

(01:26:22):
And it provides a much better context. And I think a lot of what we saw in the Cosmos web result in particular highlights how knowledge of flavonol status from an objective measure, not just a diet questionnaire, gives us more context, no different than even from the multivitamin intervention. We have many different vitamins and minerals that we can capture measure in the blood as well. And I'm actually doing some work now in that with John who's on this panel, try and understand how the multivitamin is linked with changing more objective biomarkers that capture the effects of the intervention and then how that in turn might link with subsequent risk of disease. When we're designing these types of trials and bioactives, it's critical to have this biomarker available. It just gives us a lot more of an ability to disentangle these complicated effects, complicated mechanisms that are in play.

Zan Fleming (01:27:20):
And related to that, Howard and Catherine, let's talk about one of the reasons that we don't hear about Cosmos as much as we should, and that is, as you pointed out, Howard, the endpoint, the primary endpoint was just barely missed. And you explained the difference between the attempt to treat and per protocol analysis, which really does start to answer why. And there were other factors in the trial. It happened during covid, you had higher statin use than anticipated. You had to change your endpoint to compensate for a lower effects rate of CV events. So a number of things conspired to give the trial headwind. And so to your point, when you start to evaluate compliance, you can understand why you did fall just on the wrong side of the line, the arbitrary B equals point of five, but you well could have had a positive trial and it could have been published in the New England Journal of Medicine as it should have been anyway, it was such an important trial regardless of that particular calculation. So maybe talk a bit about what happened during the trial that couldn't be anticipated and what helps us to understand why the result that we got.

Howard Sesso (01:29:05):
Catherine, do you want to start or you want me to take a stab at it first? No, I

Catherine Kwik-Uribe (01:29:08):

Wouldn't. Go ahead. It's about the trial. Go right

Howard Sesso (01:29:10):
Ahead. No, it's interesting. It actually, every trial has an interesting history to it. Every trial, not just cosmos first and foremost to your first point, I think it's interesting, and this comes up much more in lifestyle interventions than it does in a lot of the pharmacologic interventions that we do in large scale clinical trials in which the classic approach toward clinical trials is geared toward intention to treat. The belief is that it's the cleanest way to look at the data and there are advantages to that when we do an intention to treat analysis. One of the reasons why we do a clinical trial in the first place is the power of randomization. If we took everyone who's attending this webinar right now, split them up randomly into two sides through randomly, there should be balance by all the things that you can measure and all the things that you can't yet measure.

(01:30:06):
That's the power of randomization. There's always been a hesitation in the field to gravitate toward per protocol or compliance-based analysis because you start to lose the power of randomization. You're selecting those who are able to or choose to still take a randomized intervention. And for those reasons, the perceptions of the results of trials like cosmos for the primary outcomes, for example, for cardiovascular disease, for the cocoa extract intervention, get more called into question when we start to ideally show both sides of the story. And I think it's for that reason that there was a little bit of, I wouldn't quite say confusion, it was almost a mixed message. On one hand, the purists, the trials would look at this and say, well, there's no significant effect overall it's 10%, but no different than those that would look and say, well, if you actually focus on those who are actually able to take the intervention or for whatever reasons they were that a protective effect emerges, that actually happens to be on par with many of the pharmacologic tools that we already have in our arsenal to treat cardiovascular disease.

(01:31:15):
I think for me personally, I think that's been the more difficult part to reconcile is that the effect is there, how you judge it is of course a subjective quality that it came out during covid didn't concern me as much. I think the nature of clinical trial reporting and the nature of the media these days is that the attention span for most is quite short. So whether it's the results of the main trial findings or for Scott's findings for the Cosmos web or Laura's for cosmos minds or other studies as they continue to emerge from our trial, the ability for studies to stick is harder. And especially in the dietary intervention space, the food intervention space and lifestyle interventions, it's a sell on a lot of levels usually to make people understand the context of those findings. So anyway, that's my knee-jerk reaction to your important question. That's a good one, Catherine.

Catherine Kwik-Uribe (01:32:11):
Yeah, and I'll build on that. I mean, I think I'll just take, just sort of say, I think then you said it wasn't a positive fraud and I think it depends how you look at it, I think is how we just outlined. There are a number of positives. We may all agree that of course there are next steps and things that we need to do, but when you look at the results overall and you brought up statins, the reality is there was a high use of statins, there was a high use of aspirin, and by the way, the mean age was 72. The fact that even at that age with all of that background, we're still able to see a signal. Even if we consider the secondary measures of cardiovascular deaths, that number is 27% even in the intention to treat, that's a double digit, that's a big number to think about an intervention on top of all that that was going on.

(01:33:10):
And then from a per protocol perspective, the numbers just even get stronger. So there are a lot of learnings from this and lots of positives. And once again, there is safety and there's strong evidence for efficacy that I

don't think we should ignore or not consider. And then just touching back upon the biomarker, the reality is the samples, the Cosmos team and part of the trial, everyone who was part of it, there are lots of samples that are now in freezers and they can be mined. The data can be, you can continue to look at these, the trial is not over just a new phase and now they're going to be new phases of that trial. And so I think the power of the biomarker actually allows us to ask very more specific and deliberate questions, not just broad questions. So I think there were positive outcomes, lots of important and critical learnings for us, and it's only just begun with much more work that can be done really applying the learnings that we already have from the work that Harry's talked about, that Scott's talked about, that Laura's talked about. We can now actually look at the information and the data again and sort of say what else I see in my first pass that now is becoming apparent.

Howard Sesso (01:34:28):
Just I was going to say, I suppose we could also be maybe more, I mean these days the way word gets out about health studies is different than it used to. So I'm not saying that it needs to be through voracious social media accounts and postings per se, but information is digested differently today than it was five years ago, 10 years ago, certainly 20, 30 years ago. And it's difficult in a very crowded landscape of news coming in so many different directions for studies, not just cosmos. There's lots of other good work that's being done in the flavanol space and lots of other areas of research around healthy aging that finding that bandwidth and telling the story in the way it ought to be told is there's competition, for lack of a better word.

Zan Fleming (01:35:16):
Yeah. Well, and just to clarify, I think it was a positive trial, but by the standard that we applied to drug trials, it came up a little short, but drug trials are analyzed in a very conservative manner because there are benefit risk considerations. And

Howard Sesso (01:35:38):
The interesting piece to this, I'm sorry, is that traditionally in cardiology trials, what we use for a primary outcome, traditionally, if I put, I'm not a cardiologist, but I'll put on the for a moment, we use what's called a MACE outcome, major atherosclerotic cardiovascular events. And so that usually consists of non-fatal myocardial infarction, non-fatal stroke, and CVD death. We actually usually use that for our trials, but we were concerned about the duration of the trial, the impact of covid as you had alluded to before. So we actually had a much more expanded CB, D endpoint than what would typically be done. Interestingly enough, if we actually went with that traditional MACE outcome, even for the intention to treat analysis, we actually would've had a significant hit for our finding for cardiovascular disease.

Zan Fleming (01:36:26):
That's right. Those other more volition endpoints using cagle judgment tend to dilute out the effect.

Scott Small (01:36:34):
So Z, could I just add to that from Sure,

Zan Fleming (01:36:37):
Please Scott.

Scott Small (01:36:39):
Not a cardiologist, didn't do any of the work on that. But from an ethical point of view, if you both think that this is a significant finding, you leave aside and I appreciate the purists argument and dissection, but Howie, what was the effect on cardiac death? Like 27% or 15%?

Howard Sesso (01:36:59):
Yes, 27%.

Scott Small (01:37:01):
So 27%. So to your point Z, here's a dietary intervention that can reduce cardiac death by 27%, but because of the academic perhaps debate about whether it's meaningful, it's statistically reliable or not, people might not take this. So I think there's an ethical element to this academic discussion

Zan Fleming (01:37:24):
And there's another element that Catherine can comment on and that is the inability of a dietary supplement company to promote its product with information that relates to any kind of disease claim. So Catherine, maybe you could expand on that.

Catherine Kwik-Uribe (01:37:47):
Sure. So when I worked with in Mars, one of the challenges of course, and anybody who works in the food and supplement is that you're challenged with, well, your studies to date have been small, we want more, we want more proof. And then you go through the effort and you do the studies and then you're very limited in what you can say. The reality is by simply even talking about this 27% reduction in cardiovascular deaths that was observed and was measured in the trial, that becomes by FDA standards and FTCA disease claim and puts a company or any supplement at risk. And so you actually can't actually describe or technically even link to the study through any commercial materials to the study itself through any of your commercial materials, which when you talk about what's the incentive, I mean luckily Mars as a privately held company really had a long-term view in terms of wanting to understand the benefits and really seeing this out and being able to sort of say ultimately do flavonols do good and the context of cardiovascular health, it's just you're then a bit hogtied to be able to say that there actually you can't speak to it.

(01:38:57):
Yes, there are mechanisms by which you could submit for an approved health claim for the FDA, that's a long and arduous process. And in the interim, you're just actually not able to talk directly about the results without having concern of being accused of talking about a disease. And actually supplements can actually, it says on supplement boxes, this product is not intended to treat, prevent, mitigate disease, and we're actually talking about a flavonol intervention which actually may be doing those things. So you have this challenge in the current regulatory framework that really just really limits not only what you can say but how you can talk about it.

Zan Fleming (01:39:41):
Well, I think now you have some understanding why it's a trial that we haven't heard about as much as we should. Let's go now to Aine and John to talk about their broader view of bioactive nutrients and what stand out as other agents that you think should be run through a cosmos like trial, and are we ever going to see these kinds of trials being done? Is that just again, a unicorn, which it's not going to be done because they're not commercial incentives?

Aedin Cassidy (01:40:18):
Yeah, I mean there are many other flavonoids where certainly the flavonols are ahead of the game, but there are other flavonoids where the evidence is mounting to, again, from all of these sources, from mechanisms of action through to large population-based studies and trials. I'm thinking particularly of the anthocyanins that are in berries responsible for that lovely red blue color that you get in berries. But I think Scott's study has shown that background levels are important, but probably what's really important is understanding. We know when we eat them that people metabolize them differently. So wide inter-individual variability, and we really need to start to unpick that. And I think Cosmos is a perfect example of

being able to do that because they have this lovely biomarker of FLA and three ols. Is it genetics? Is it the gut microbiome? But we know that when we feed the same dose of flavonols or other flavonoids to people, you get variability in the response, be it blood pressure lipids or in Cosmos case in events, and can we disentangle that and then can we help people metabolize them better? So that that's the big area. That's the next step that we really need to understand and cosmos will really help us to start to unravel that for this important class called the flavanols,

John Erdman (01:41:51):
I think there are two dietary bioactives that are far ahead of all the rest and flavin three alls are number one. Number two is lutein, zeaxanthin and age related macular degeneration. There are a lot of trials on both sides. We've heard the ones starting from Catherine and through Cosmos on Flamm three oils, but there are NIH studies and many other funded studies on reduction of macular degeneration, increased macular pigment from lutein in foods and supplements. So those two are far ahead of all the rest who funds some is an issue. Most food companies are not like Mars, they don't look years out and they don't have the capacity to fund these trials. NIH may or may not help fund it. They did in this case help fund this trial, but in many bioactives they're not liable to do that. I want to also go back to your first question Z and the benefits. So the White House conference that was held a year ago out of that came a mantra as food as medicine and NIH has initiatives on food as medicine. This is an example of food as medicine. If you look at the data in one way from the Cognos, trial was good as statins. Actually I prefer food, not medicine is a better mantra, but I'm not sure that'll carry the date.

Zan Fleming (01:43:56):
Well, thank you, John. That's great. Thanks to Doug Ke and our audience who points out that FDA has allowed a qualified claim for flavanols and it's a pretty parsimonious claim. It's not a ringing endorsement, the read it's risk of cardiovascular disease. Well, the OL flavanol powder may reduce the risk of CV disease, although the FDA has concluded that there is very limited scientific evidence for this claim, so not a ringing endorsement that's fairly not going to sell a lot of product. But

Howard Sesso (01:44:41):
The reality is that every qualified health claim that's ever been approved by the FDA tends to still have all the qualifying language put into it. And especially in the nutrition landscape, there's always some inherent distrust for whether specific nutrients or dietary patterns to a certain extent, and certainly specific bioactives might somehow be mechanistically responsible for a specific benefit. So it's just a good example. And of course, how do you define very limited? Is it on the basis of the lots of smaller studies or few small studies or is it one larger study? It's not to say that bigger is always better, just because cosmos is big doesn't make it better. It's really cosmos as a whole that makes it what it is that I would argue has greater validity. I wouldn't really argue it's one and done, but at the same time it still is a very large leap forward in terms of what we understand specifically about FLA and three alls as a dietary bioactive as well as the role of the multivitamin and the various outcomes that we've looked at there too.

Catherine Kwik-Uribe (01:45:52):
I think just building a little bit upon that, I think the health claims are just one way you can communicate to consumers. It's not the only way. And I think Aine talked earlier about the AD recommendation. They came out about a year ago at this time, and so that's out there. And so once again, there are multiple ways to get the word out and to begin to advise, and I think this is where the opportunity is. Health claim is one and may not be the holy grail quite honestly. It really actually could be many other ways of doing so, and I think it's in part us the ability to consider what are the other ways in which we want to get these messages out to consumers, to the friends and family, those people that we love and we really do believe can benefit from what the science and the research is telling us.

Zan Fleming (01:46:40):
Thomas, you've got some questions I'm sure to feed the panel.

John Erdman (01:46:48):
Sorry,

Thomas Seoh (01:46:49):
I had to unmute. I saw a question from Todd in the q and a and I think maybe there was, Leslie had a question about another indication or use of supplements, but I guess I see that it's considered answered. It's true. It is. A question I guess I have is that this is a terrific advance to have the Cosmos trial. How easy is it for applying the learnings of genetics to bring more people along or is it something that's very, very practically very difficult given the nature of large nutritional studies?

Howard Sesso (01:47:34):
I mean, I can take an initial stab at this. I think it's interesting. I think in this world of perhaps too much information and too much data, which is supposed to be a good thing, but it still is a good thing. One thing that we have not really tapped into and it's being discussed more is this notion of either personalized nutrition or precision nutrition. The idea is that if we're looking at a trial like Cosmos or other large scale trials or other smaller trials that have been done, can we better hone in on those that might benefit more from that given dietary intervention, whether it's a cocoa flavonol supplement or otherwise versus those who might not benefit quite as well. Genetics is one tool to do that. It's not the only tool. In this day and age we see things like just to name a few.

(01:48:23):
I mean we've metabolomics, we have proteomics, we have catalyst, other ways that we can generate data, and this is where artificial intelligence, machine learning can probably take these data more in aggregate and try to help tease out and better identify or personalize to some extent who might benefit more from an intervention versus another because it doesn't tend to be a one size fits all proposition. In reality, and we see this from all of the studies that we've collectively done, not just in Cosmos, but other large scale dietary interventions that we've done over the years too.

Zan Fleming (01:49:02):
On the other hand, these test and AI drive cost, and that's the big issue for doing large outcome trials. We need ways of getting relevant or salient information without the expense that is frequently associated with a cardiovascular outcome trial. And I think web and nine, those sub trials are actually exemplary of the kind of tools we need that can be more cost effective and getting evident that something is being improved or not. Speak to that, Scott, and what's the future of web-based neuro function test and outcomes that ultimately be validated as a regulatory endpoint?

Scott Small (01:50:08):
Right. Well, I'm not one who likes Silver Linings, but one of the silver linings of covid is that the whole practice of aging and dementia, my subdivision, my division within neurology was forced to learn how to do home-based assessments and neuropsychological testing is the core of those tests and they've now been in many ways translated to be done at home. There's a lot of advantages to interviewing a patient at home. You get to see their, where they live, their family, their kids, grandkids. MRI is another, if I just go down the lists of tests, we use MRIs becoming mobile and miniaturized to potentially be delivered to someone's neighborhood. Phlebotomy is a challenge, but if I can just speak to my field in Alzheimer's disease, the move now is, I'm sorry, spinal taps, lumbar punctures are a challenge to do home base, but most of the biomarkers that we're now relying on to diagnose or exclude Alzheimer's are soon to be plasma. So I do think that in my field, a lot of it can be done at home. Obviously for certain other specialties like

orthopedics, I think hands-on the patient is critical, but I do think Covid has forced everyone to realize that medicine could be practiced with the patient at home.

Zan Fleming (01:51:55):
And relatedly, what about digital apps that we had a question about the utility for measuring function. For example, gate speed can be done with a cell phone.

Scott Small (01:52:10):
Yeah, that's at the cutting edge, that's bringing in AI and that's going to actually do better than us according to some people. If I can record your mobility as you type on your cell phone, I can listen to subtle tremors as you speak. That is the future. There's no doubt, home-based digital diagnostics. So that's upon us and that's going to sweep through that throughout the field even more and more.

Zan Fleming (01:52:43):
Laura, what about what are you seeing on the cutting edge of technology that could in one way or the other, improve our ability to measure benefit? And you're on mute.

Laura Baker (01:52:59):
So I'm a fan of technology for measuring passive activity for sure, but I'm just going to get raise the issue again of marginalized communities. It's just true. I have a little fear that our move to that if we go too quickly without the trust is it's one more way that we will separate the haves and the haves not and the have nots. So I think we can't just push forward because it's a great idea. We have to make sure we're inclusive all the way. A lot of my work is making sure that we can get out in these communities and start building trust. And I think the science and the building trust has to go hand in hand. So I know I sound like I've said this before, but I really think as a scientist, our way forward has to be part of that solution, has to be how to engage more communities that have been left out of the clinical trial picture for years.

Zan Fleming (01:53:56):
Nadine, are there digital apps that allow you to allow people to determine their nutrient intake to otherwise improve estimates of what people are eating?

Aedin Cassidy (01:54:12):
Yeah, there certainly are. And there's been huge developments in terms of biomarkers of nutrient intake too, particularly using metabolomic approaches. But the big issue is the kind of validation and evaluation of those to make sure we're measuring the right thing. I mean, and the flavonoids are a perfect example. They've got a very short half-life, so you need to know what is the key metabolite that you want to measure, otherwise you could miss it. It depends when you last ate it. So there is advances there, but not as advanced as you would like. Particularly for nutrient intake, we're still reliant on food frequency questionnaires. What did you eat yesterday? Please fill in this diary, albeit on a web. But I think we do need to move to more sophisticated methods, but then it's evaluating them against what we believe are the gold standards at this moment in time.

Scott Small (01:55:05):
Although I would say it's not quite digital, but the urine based GVLM test is potentially a home-based test. It's exciting.

Aedin Cassidy (01:55:12):
Yeah, absolutely. Yeah,

Howard Sesso (01:55:16):

I mean, the challenge is that diet is so inherently complex and measuring it. I mean certainly the food frequency questionnaires that have been historically used, not just out of Boston here at Harvard, but in other large scale studies have their strengths in getting at the relative intake of foods and dietary patterns and nutrients, but it doesn't really get the type of specificity that those of us that are in the field would really want to have. And we're trying to translate those into meaningful dietary recommendations, thresholds of effect, thresholds of benefit. What's interesting in the app space right now is that there are several apps that are being developed that are trying to have you take pictures of the foods and then trying to translate that into serving sizes and nutrient composition. But as you can imagine, again, diet is not just inherently complex, but it's inherently personal.

(01:56:06):
Everyone has a very personal attachment to the foods and the beverages that they eat or drink. And again, this is not to say that we shouldn't try to continue to revolutionize how we do dietary assessment, especially in the context of healthy aging. But more to the point, these biomarkers, these more objective biomarkers of intake, if we can do it in a way that it's scalable to a larger swath of the population, has a much greater potential for public health benefit. And so I think whether it's in the context of Flavin three, all guidelines that are trying to be put together, linking that with a way to actually capture flavonol status quickly and efficiently is a critical part to make something like that really stick, whether it's in the context of cardiovascular health, cognitive health, or otherwise.

Zan Fleming (01:57:02):
Great. Howard Thomas, any other questions you've got to put up?

Thomas Seoh (01:57:09):
I've not seen them, but I was interested in amongst the entire panel what you view as the final terms of the significance and the promise of the trials. Because sort of being in the audience, I've learned a tremendous amount of facts. I'm trying to understand how to think about it in terms of significance and promise for the future.

Zan Fleming (01:57:39):
Well, let's take the primary endpoint on the CV endpoint. Is there a consensus that we see a persuasive effect from Osmos that would support the benefit risk decision of or benefit risk relationship for taking the flavanol product? Don, you want to take that?

John Erdman (01:58:14):
I think Catherine already pointed out and how we can elaborate. There weren't adverse events. So if you look at risk benefit, it appears to be all benefit for a significant portion of the participants, especially those that consume the product.

Zan Fleming (01:58:39):
Yeah, great point. And likewise for the multivitamin, we have pretty persuasive evidence, two different studies showing a benefit. Is everybody on a multivitamin?

John Erdman (01:58:55):
No,

Zan Fleming (01:58:58):
You're not, John.

John Erdman (01:58:59):

No.

Zan Fleming (01:59:01):
Well, is the evidence not persuasive to you or are there some other considerations?

John Erdman (01:59:08):
Well, no. Being trained in nutrition for this long of a time, I believe in the food approach first. I think my diet, my wife is also came through a dietetics background, so we eat very well. So I don't take a multivitamin.

Zan Fleming (01:59:30):
Okay. I think I We'll start doing that. What about you?

Howard Sesso (01:59:38):
Yeah, I mean I get this question a lot, admittedly just with my work over the years, especially the multivitamin side don't, again, I kind of go with the food first approach, but at the same time as I get older, as I go in my fifties now as I get into my sixties, seventies, or however long I last, the type of research understanding how the effects the contextualization of those effects. So if we see, for example, for the multivitamin that the effects for on cognition might stick even among those that eat well or eat a balanced diet well that's information that becomes a little bit more translational. No different than if you put that in contrast. What's interesting in Cosmos is that about half of the participants came in, almost half came in already taking a multivitamin. We asked them to stop and they fortunately did, at least we think they did based on what they reported

(02:00:37):
For the cocoa extract. Supplements a different type of question because we know that it's not as if a large swath of the population are taking any type of cocoa extract supplements. There's other perceptions about cocoa and flavanols in the cocoa space. That's a whole other complex issue. But the key for flavanols really revolves around the fact that it's a plant-based food. It's a plant-based source to those foods. So it's not just cocoa, it's berries, it's red wine, it's other healthy food choices. And supplements could be part of that equation for many people, but it shouldn't be the only option per se either. So it's really understanding the bioactive component or those individual vitamins, the individual vitamins and minerals that really matter. So do I take a supplement? No, but could that change over time? Certainly. I'd like to think that I'm somewhat open to change if need be.

Zan Fleming (02:01:33):
Adeem, how about you? What is your approach again, first

Aedin Cassidy (02:01:39):
Trend and nutrition through and through. So very much a food first approach at this age.

Zan Fleming (02:01:45):
Alright, well I like the idea. I don't see the downside. I guess in theory there could be, but at the very least it looks like there some positive effect and cognition. Would you say, Scott, would you agree?

Scott Small (02:02:05):
It's interesting to hear everyone's biases in favor or against I am trained mechanistically. The one thing I like about the Flavanol story is that there is more replication, consistency, animal models, multiple studies, and to a certain degree mechanism. If the dent h iris is the seat of cognitive aging, rusty and his original study show that it induces angiogenesis in that area. We then replicated that in our human studies. We know some mechanisms for why that would be, that all hangs together to encourage me if I were flavonol

deficient to take it with the multivitamins. I also eat very well, and it just seems a little bit lacking in mechanism, which is an admitted bias of mine.

Zan Fleming (02:03:04):
Alright, fair enough. We have a question from Michael Zibell, our chief scientific officer Nixon, who it's wondering if the response to multivitamins is in some way more due to low BMI or it's overrepresented among low BMI patients or people, sorry subjects.

Laura Baker (02:03:36):
So yeah, there's a message in the chat about that. But in our multivitamin study, we did several, I didn't mention this. We did several subgroup analyses to try to see who were our responders, and one of our subgroup analyses was by BMI. So I can't, and in that analysis, first of all, we saw that it didn't matter whether a person had low BMI or high BMI. They responded equally well to the intervention. There was no treatment effect by BMI. We also looked at just in cases as related, we also looked at people who were prior multivitamin users versus those who were not at baseline. Again, no difference in response, which is kind of throwing a lot of nutritionists for a loop because you think, well, it all has to do with who's already eating a healthy diet. Those are going to be, that's going to differentiate the groups and we're trying to look at that in our analysis and deeper dives. And so far we're not seeing it. We actually even looked at diet quality. The parent trial shared this with us. When people filled out questionnaires about their diet quality, we found that there was no interaction between quality of diet, low, medium or high at baseline and response to the intervention. So I think it makes sense to say that those who need it most are going to respond most, but that's not what our data are telling us.

Zan Fleming (02:05:06):
Dean and John, do you have a sense of the degree of deficiency or let's say relative depletion of flavanols there is in the general population and maybe it's very much a regional phenomenon. What would you say would be a expectation of making flavanol available to people who are identifying people who are sort of flavanol deficient?

Aedin Cassidy (02:05:42):
Yeah, I mean, if I start on that one, well, the mean daily intake of the flavanols in the US is 200 milligrams a day. Now obviously there's a huge range in there, but yet the optimal intake is thought to be two and a half times that 500 milligrams a day. It's quite a way off.

Zan Fleming (02:06:03):
Where are people consuming more optimal levels of leavens?

Aedin Cassidy (02:06:11):
You mean in what parts of the country? I don't,

(02:06:15):
But in terms of sources, it's quite different across country. So in Europe it's tea is the main source. I can't remember what the main source is in the us, but it's most likely something like apples and pears, not necessarily chocolate and cocoa, which actually isn't very well represented in some of the questionnaires that are out there. So yeah, levels are very low in the community and the cohorts tend to be, like Laura says, they tend to be the worried well as opposed to the disadvantaged communities again. So we aren't looking at the hard to reach where if the mean is 200 in the worried, well, you can imagine where the levels are in those other communities.

Scott Small (02:07:03):

I also say it's not just space, but it's also time. Isn't there a seasonality to the flavanol consumption? I thought I saw a paper to that effect, which would,

Aedin Cassidy (02:07:16):
Yeah. Yeah. I don't know, but I'm sure there is. Yeah, because a lot of it comes from a range of fruits as well,

John Erdman (02:07:25):
So grapes and things would be down. So yeah, I think places like UK and the Netherlands are quite in overall flavonol intake, whereas US is pretty poor. We don't consume fruits and vegetables. Some people may be getting it all from red wine, which is maybe not the greatest idea.

Howard Sesso (02:07:52):
Well, I think the other concern is also affordability. So you think about some of the food, so if you use berry intake just as an example, I mean I think certainly the various types of berries are good sources of flavonoids as well as flavonols. And yet for those of us that go to the store and regularly try and purchase berries, there's seasonality to the product where it's coming from and the price goes way up and down. Or if you're choosing organic or non-organic, I mean, there's lots of factors. And so speaking back to Laura's point about trying to emphasize not just the flavanols and other potentially beneficial bioactives for healthy aging, we've got other challenges that come into play with recommendations in terms of whether those recommendations are even translatable into those most vulnerable populations that don't have the luxury of Sam's going to go purchase a few pints of blueberries or some other food as my source of flavonols.

Zan Fleming (02:08:51):
Well, this has been an amazing discussion. I have learned so much myself and I know our audience has as well. I can't thank all of you enough for hanging for two hours and the preparation that went into that. It's going to now be time for Thomas to ring the bell, but let me just again thank our audience for participating and we'll follow up as Thomas will be telling you in a moment.

Thomas Seoh (02:09:23):
So again, a link to the recording will be sent to all registrants within a day or so. Please be on the lookout for a notice for part two, which will focus more on the cognitive findings of Cosmos Web and mind, as well as other indications that may be publishing in the future. And we are keeping the room open. This is the end of the formal presentation, but for those who are totally optional, we're able to stay for a little while to mill around. We try to recreate the physical conference where people will come off the DA and interact with the audience and so forth. You're welcome to do that for a few minutes. We won't close the room out abruptly right now, but with that, I thank everybody and wish everybody a great weekend.

Zan Fleming (02:10:10):
Thank you.

Thomas Seoh (02:10:15):
I just want to say by the way that I started to take Centrum multivitamin as a result of the theory that can't hurt, could help. And from the standpoint of great nutrition, which all of you knowledgeable people are able to effect to Laura's point, not everybody will. It's a bit of privilege, I guess, to have that knowledge and the means to be so well nourished. And I am a little bit biohacking in terms of intermittent fasting and keto and so forth. So supplementation to me, it seems like so long as it's reasonably safe, can't hurt, could help. But just thought I'd throw it out there for any general free for all if people want to pile onto me or to give me a validation on my,

Howard Sesso (02:11:05):

Well, you're a good example, for better or for worse, where a lot of times people start taking various dietary supplements, other bioactives more broadly under the perception of well, it couldn't hurt to take it. And then if they start taking it, well, I haven't dropped dead, I haven't had other things that are obvious warning signs to why you shouldn't be taking it. So the perception that it couldn't hurt is a little bit of a misleading once we don't know whether you're actually benefiting from it, some people will swear by it. There's a whole other placebo effect that can sometimes be in play. That's a whole other fascinating topic. But the one thing that's nice about the trials, not just Cosmos, but others that have been done in this space, is that it showed quite definitively that any concerns, at least with respect to on the safety side, it showed quite strongly that there shouldn't be any safety concerns.

(02:11:59):
That doesn't necessarily mean you should just automatically be taking a cocoa extract supplement or multivitamin per se, but at least from a safety standpoint, I think Catherine made this point on a few occasions earlier that was just as important as any of the efficacy findings that we're reporting. Because even for most of the things that are out there on the market in the supplement space specifically, we don't have the luxury of having these large scale trials evaluate them. And we don't know how they interact with different medications, other foods, other supplements that one might be taking.

Thomas Seoh (02:12:28):
But Howie, just to be clear, if I'm adding multivitamin, are there significant safety questions about that? That's the basis of my saying can't hurt, probably could help.

Howard Sesso (02:12:40):
There shouldn't be. But even if you look within the multivitamin space, I mean if you just go down to a Walgreens CVS or some other store, I mean it's dizzying how many options that you have. And there are many multivitamin formulations that are out there that start to mix a lot of things that are not necessarily your essential vitamins and minerals. So usually for me as a general recommendation, I try to shy away from those because we don't know necessarily what's happening there in terms of potential interactions with other, whether dietary interactions or other medications. So for me, I always prefer to keep it really almost simple in terms of the choices that you might consider if you're going to take not just a multivitamin, multi mineral supplement, but other types of supplements, just keep it to more of the tried and true, the larger suppliers, the ones that you have a little bit more faith comparatively in terms of safety as opposed to a lot of the other people that just kind of jump into the market.

John Erdman (02:13:36):
And the dose issue is very important. So I had a woman referred to me from town here who had eye problems and she ended up with vitamin A toxicity from taking too many vitamin A supplements. So on these multivitamins, I'll say percent of DRV or daily value, when it's three or 400 or a thousand percent, you got to think about it.

Aedin Cassidy (02:14:08):
And the current evidence for the flavonols is the same. It's not linear. The more the better. And it seems to be that about 500 mgs a day seems to be the optimal for these.

Thomas Seoh (02:14:20):
That was a question in some of the questions that came in with the registration. How did you determine the dose and with more have been better?

Howard Sesso (02:14:30):

This is the biggest problem that we have with these large scale trials that we're basing the judgment on the 500 milligrams per day of the Coca Flavanols based on the best available evidence when we were planning the trial back in the mid 2010s. And the danger, the concern that we always have with these trials, not just Cosmos, but others that I've been involved in over the years, decades, is that you hope you make the best judgment for what you're testing in terms of an amount for your particular bioactive or supplement or what have you. Because don't know, 6, 7, 8 years down the road, what's the current science? Are they going to evolve to suggest that there's risk perhaps with the amount that you're testing or it's not enough? So typically when you're trying to figure out the amount that you're testing in these types of trials, you don't want to go excessively high. You don't want to go excessively, let you try and do a bit of the middle ground, but it's honestly a no win situation from a trialist standpoint because no matter what you do, someone can find criticism in that. And that's fair criticism, right? Oh, you should have tested more. You should have done a three arm parallel arm trial, right? You should have tested 500 and a thousand or some other higher amount.

Laura Baker (02:15:43):
The dose is always wrong. It's always wrong.

Thomas Seoh (02:15:46):
Always

Howard Sesso (02:15:47):
Wrong. Exactly. So you go with the best science at the time that you're developing that trial and that trial protocol and you kind of hope for the best. It's a bit of And safety, a bit of a leap of faith. Yeah, exactly.

Thomas Seoh (02:16:02):
I noticed in your answer, Howie, to the question of what was the vitamin used? You referred actually to Centrum in the formulation in the 2010s or so, which was a fine point I never thought about. I am taking current formulation of Centrum and I don't know how it's changed over time.

Howard Sesso (02:16:21):
They changed a little bit over time. The multivitamins don't change, typically change massively. There's tweaks. So they might, and inherently most of the common multivitamins that you might see in the market are more geared at lower amounts of each of the vitamins and minerals as opposed to a mega dosing with an individual supplement that you might find. So it might be a tweak up or down. It's not usually an, and the hard part, which we didn't really cover with multivitamin and multi minerals for formulations in particular, is that from a mechanistic standpoint, you're kind of left in the dark. Because if you think about a typical multivitamin, you've got, let's just say roughly two dozen individual vitamins and minerals packed into that. So if you see a benefit on cognition, what's driving it? It's a little bit of an easier question to answer when we're looking at the cocoa extract supplement of, well, maybe not easier, but comparatively easier for the cocoa extract supplement in that we have a better way of knowing what's in it, quantifying it, and a biomarker that goes alongside it much more directly. But for the multi multi mineral formulation, what's driving it is it the vitamin D camp will say it's vitamin D, the magnesium camp will claim it's magnesium. It's a little bit harder to evaluate from a mechanistic standpoint. Still

Laura Baker (02:17:45):
Needs to, yeah. And how, I know very rarely is there conversation about synergistic effects. One plus one is not always two. And so that's really a big issue. And this is really, I just more work needs to be done in this area. Most certainly

Zan Fleming (02:18:03):

Chance,

Laura Baker (02:18:03):
I just wanted to say Centrum Silver too. The one that we use, what I've been impressed with, and I have nothing to do with Centrum Silver, nothing is they have a very strong scientific advisory board that helps them revise their formulation on a regular basis. And these people include people from the cancer, from the cardiovascular world, from the Alzheimer world, if for nutrition, of course. So it's just, I think the question I get all the time is the generic brand just as good as the other brand on the shelf. And I think you really do have to consider, I've learned there's so much that goes into creating a multivitamin that there's a lot of instability of the individual micronutrients while they're combining them. And if the company's not careful about the instability, you get an inert substance. And so I think it's just we really need to provide more education to the community about this kind of thing.

Zan Fleming (02:18:56):
Yeah, that's a great point, Catherine. I wanted to go back to voter term studies that Mars has sponsored that show benefits on cognitive function. In other words, real improvements in cognition, necessarily disease modification, but nonetheless improvements in measures of cognitive function.

Catherine Kwik-Uribe (02:19:22):
Yeah, and I think also welcome Scott to jump in. I mean, I think when we started looking at some of the cognitive benefits, as I think I said earlier, there was more of a global approach looking at multiple tests. And some of the original studies which were done in collaboration with partners in Italy, we had studies done in an older population. I think the mean age was in the range of 75 plus a much older adult population. Some were cognitively intact. And we also did some work in individuals with mild cognitive impairment. And both of those studies over the course of eight weeks being able to see significant improvements in sort of a cognitive zco. At that time we didn't have the biomarker of intake, so very limited to know really what the background diet was. We assumed it would be relatively high given where they were living geographically.

(02:20:19):
And it wasn't specific. And I think really it was the work that Scott had started and in collaboration there that we were really getting into understanding both from preclinical models and understanding that the hippocampus was the hotspot where a lot of important things were happening. We were actually from the preclinical data, seeing some important morphological changes there as well. And then it really led us to do the several studies with Scott and the team looking specifically at cognitive function. One of the first studies was included a model of exercise, but as we went forward, really looking more specifically an older population but cognitively intact and really beginning to see these effects on hippocampal dependent aging. And the study prior to Cosmos really beginning to hone in on the fact that background diet was having an effect or something that really could have an effect as well.

(02:21:18):
And so once again, it was this building of data that there is from a vascular perspective and then to a cognitive perspective, there was evidence of these benefits and then really beginning to hone in on where those benefits were most prevalent and mechanism of action underlying it. And now we come all the way to Cosmos, which is now we're putting together all the pieces from the preceding stories, longer duration, larger trial, putting in the biomarker of intake, also layering on top of that the information as it relates to the diet, as measured through the alternate healthy eating index. And then looking in totality at the cognitive performance. And I think overall what we're seeing was again, is this evidence that flavonols are having an effect. Background diet is an important variable to consider, but in those who are low in flavonol intake, we do see these very pronounced improvements in cognitive function.

Zan Fleming (02:22:19):
Well, gosh, we can keep going. I probably we should come to an end. But again, what a great discussion and thank you for hanging late. It's been two hours and 15 minutes and we much appreciate it. I know the audience

Thomas Seoh (02:22:44):
And we look forward to doing this again in a few weeks, at least among the people who are on the panel still. We will look forward to focusing on the web and mind the cognitive aspects in the next session. So thanks everybody. We're going to close up the room. But thanks for sticking with us, those of you who are out there. Bye-Bye

Zan Fleming (02:23:09):
Bye.