Dr. Rick Ferris Interview
Conducted by: Dr. Kupfer and Mr. McManus
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Dr. Kupfer: Rick I wondered if we might begin at the beginning and have your feeling on what was the attitude of clinical trials amongst research establishment as you saw it. You were coming in also at a very early time and had a viewpoint which was very strongly influenced by statistical information. And you were going to be hands-on with the mechanisms and the wherewithal of the clinical problems. What were your feelings about the feel at that time?

Dr. Ferris: Well, I came right after my internship in 1973. So I had just finished a medical intern ship at John's Hopkins and all of the post grad interns felt particularly well trained at that time. The funny thing is the definition of what well trained is. But we had worked very hard and I was coming to something totally different. Totally different from my medical training but not different from the experiences I'd had in Educational Testing Service where I had been doing statistical analysis for various educational studies. They weren't randomized trials, but they were similar. Although randomized clinical trials were being done in the 70s, many clinicians felt that these were an intrusion on their practice of medicine and I think that it was really a problem for them. In addition to issues related about getting support for randomization, it became clear to me that the outcomes that we were talking about for the diabetic retinopathy study really hadn't been completely thought out. As the Diabetic Retinopathy Study evolved, the focus was how do we do this study and not so much as the details regarding the outcome. I remember it, "blindness" was the stated outcome, but there wasn't even a clear definition of blindness. I remember talking to Dinny Davis about the details. At that point I don't think any of the details were specified; the chart type was unclear, although it was probably thought to

be a Snellen chart and the details of how the exam was done were not specified. I had a little bit of background in ophthalmology at Hopkins in medical school but I was certainly a baby in ophthalmology. As we developed the specifics the level of acuity was defined as the lowest line read with one or two of mistakes. And I remember saying, well I guess everybody has 20/200 patients because there's only one 20/200 letter, so you cannot have two mistakes on the 20/200 line. Then we developed a chart that had four letters one each line from 20/200 up to 20/800. Then we tried to define how to find the best corrected visual acuity and how one would measure visual acuity in a research setting. The strong sense of the group was that this should be measured by the best person who could possibly do it and that was thought to be the ophthalmologist in charge. My job early on in the Diabetic Retinopathy Study was to perform site visits. A major goal of the site visit was for me to talk to all study personnel to assure that this carefully written out protocol was being followed by everyone. I remember going to one of the clinics for the first time as a solo site visit after the goals of the site visits had been worked out at a number of site visits performed by Dinny Davis and Fred Ederer and me. At many of these visits the three of us went we really went for just one day. At this first solo visit I thought I'd better go for a couple of days because I can't do everything the three of us were doing in one day. I eventually realized that if you went for one day, you got what I started calling the show. A clinic could put on a show for you as to how they were doing the trial. But if you were there for three days, eventually things went back to "normal" because it was difficult to keep the show going that long. In three days, we would get to see both whether they knew how to do the trial according to the protocol and it between the show part and eventually, later we would see how they really did it. I remember on one site visit that the PI did one of the most elaborate refractions that I had ever seen. He was absolutely meticulous. And we wrote it down and noted what a wonderful job he'd done. The next day, or the day after, a study patient came in and

needed a refraction but the PI had gotten a call to go to the operating room. Then I saw the fastest refraction I'd ever seen. That led to extensive discussions among the DRS executive committee and the Eye Institute about the best and the most reproducible way to do visual acuities, and about the importance of having consistency of measurement. It was agreed that it was better to have consistent good measures of visual acuity than to have the best possible measurement if you can't attain that level at every visit.

Dr. Kupfer: Let me just ask you, there were 15 clinics I believe. Who do you think came forward to advise to do this and did they really know what they were getting themselves into? Because I thought it was very impressive that among the original 15 and you remember Charlie Campbell at Columbia backed off because he'd said this treatment was beneficial and he just couldn't handle it all.

Dr. Ferris: Ed Okun also felt that the treatment was so beneficial that he could not randomly assign eye to no treatment so he never applied but he did help with the study design.

Dr. Kupfer: Ed Okun never even applied, but that's okay. But the 15 really stuck with it and that's pretty impressive. Did you have any thoughts about what their motivation was at that time? Because they were running against the flow.

Dr. Ferris: Yes, but I think that a lot of them had participated in an earlier symposium. I think they were truly interested in understanding diabetic retinopathy and whether the treatment was effective. I think a lot of them knew about the ongoing Heart and Lung trials and were also interesting in participating in this "new" type of clinical research.

Dr. Kupfer: And Cancer was doing some.

Dr. Ferris: Cancer was doing trials and I think there was an interest both in the clinical question and the methodology. Maybe this new Eye Institute was going to develop some methodology that hadn't been widely used before. That Arnall Patz had done a clinical trial more than a decade earlier and Arnall was an influential person in this group. Among the influential people were Arnall Patz and Dinny Davis. Dr. Davis was

excellent for the job as study chairman in part because he paid so much attention to Fred Ederer and he was willing to listen. He was not a dogmatic clinician and he knew the right thing to do was a careful clinical trial. He was very much uncertain about whether was effective and willing to listen to how to best perform the trial. I think the fact that Fred Ederer had come from the Heart Institute where they had been doing trials helped.

Dr. Kupfer: And previously from the Cancer Institute.

Dr. Ferris: Right. At both institutes they had been doing what would be recognized now as good clinical trials. I think that was a major reason that the study investigators wanted to participate in this new effort. They wanted to see it work, and I think a lot of them were very skeptical about it working. I remember talking with one of the DRS PIs one of them who thought the treatment was ineffective, flashing lights in eyes to save them from diabetic retinopathy. I think it's important to remember that there really was equipoise in the community that as to whether photocoagulation was effective. Remember that Lloyd Aiello had been virtually laughed off the stage for doing his scattered polka-dot type of treatment.

Dr. Kupfer: Do you recall, is it correct that Ed Norton refused to have photocoagulation done at Bascom Palmer?

Dr. Ferris: Bascom Palmer was one of the most skeptical sites and I think what Ed said that the only way you could have photocoagulation there was within the clinical trial. And he felt very strongly that if treatment was effective it would be best to demonstrate it by a carefully done clinical trial. I think the fact that Ed Norton, Arnold Patz, and some of the truly big names in retina that were advocating the study, even at a time when other people were saying that it was impossible to do a study on diabetic retinopathy because it was such a diverse disease, that gave the study the impetus necessary to make it successful. Critics were so focused on the severity and diversity of the disease that they thought it meant a trial was impossible. I think that actually showed the lack of understanding of the power

of a randomized trial. The diversity across the two groups wasn't necessarily a bad thing; it could be controlled for within the trial.

Dr. Kupfer: Was there a very strong interest and knowledge about the Retrolental Fibroplasia study that Arnall did to show that he can really come up with the answer in a relatively short period of time in a very major serious condition.

Dr. Ferris: I think that was in the background and I think the fact that because Arnall Patz would only talk about his study as just a little trial that was nowhere as good as this new trial helped keep everyone focused on success.

Mr. McManus: Earlier you said that the participants wanted to learn more about the disease than the disease process. Did they really understand at that time how much they could learn about natural history and other things with it?

Dr. Ferris: Absolutely not. I think that one of the big lessons in ophthalmology that was learned was how valuable the natural history information is to understanding a disease process. So, when we talk about justifying the cost of the trials we have to keep in mind we learn much more from them than whether treatment A is better than treatment B. It is easy to look backwards and say that we knew that laser treatment worked, but I can tell you from visiting various clinics that most of the study ophthalmologists were not sure. Some, such as Lloyd Aiello, did think that laser treatment worked and that could be measured by the fact that he was not enrolling patients with neovascularization on the disc into the study. I remember Dinny Davis going on site visits, particular clinics where he thought that the recruitment ought to be better and discussing the reasons for slow recruitment. Dinny thought that even if you really believe the treatment was beneficial, the careful clinical trial was the only way to convince people. He talked to Dr. Aiello about the trouble he had convincing people without the clinical trial that the treatment was helpful. I think that was correct and when the study results were released it was the fastest way to a consensus. The other thing that I was impressed with when the results were announced

was the general acceptance of the results. I remember discussions you had with Julian Morris, the head of the Information Office, about the responsibility NEI had to publicly disseminate the study results. Of course I think most researchers did not view this as part of the job. They viewed the dissemination responsibility to be simply the scientific publications and presentations. Since then we have learned that public dissemination of study results is a major responsibility.

Mr. McManus: And diabetes there had been a lack of understood knowledge of people who had diabetes and a lack of knowledge of treatment, early treatment centers.

Dr. Ferris: It was important that we switched from just talking to clinicians to also talking to the public. If patients know about effective treatments then they will talk to their doctors about them. We learned that it was important to let the public know the study results and certainly now that's a major aspect of any major clinical trial.

Dr. Kupfer: Now you referred in your note to me at the end of the sort of controversy at the end of the trial. My memory obviously is very biased and I would very much appreciate if you would give your recollection of why I felt so uncomfortable about stopping the trial.

Dr. Ferris: We learned a lot about data monitoring committees and policy advisory groups from the DRS. At the time of the DRS the idea of a data monitoring committee was pretty new. The experience with the University Group Diabetes Project (UGDP) had suggested that it may be important to have an oversight committee in addition to the DSMC. The DSMC in the UGDP stopped that study early because of an apparent increased cardiovascular risk. That created a storm of controversy. Because of this I think there was some rationale to have a policy advisory group to make sure that the data monitoring group didn't run amuck. They could give you needed expert advice. As the data were accumulating in the DRS I was fortunate enough to be the executive secretary of both the data monitoring committee and of the policy advisory group. I had the opportunity to work directly with Drs. Jerry Cornfield and Abe Lilienfeld. Boy, were those two pretty

good people to learn from. So, as the data were accumulating the DSMC noted a statistically significant treatment benefit developing. The statisticians were getting pretty nervous because the p values were getting pretty impressive. This was before the days of pre-determined stopping guidelines such as those devised by O'Brien-Flemming. I don't think that there had been a lot of discussion in the DSMC meetings about when they would stop until they started seeing these extreme results. These results certainly generated heated discussion. The discussions went as they still do in data monitoring committees. Some feel the results are pretty extreme but it's still early and there might be later changes. Others feel that we cannot afford to continue to wait without offering an effective treatment to the patients. It was decided to look a little bit longer and the decision to stop the study was put off for another meeting. At the next meeting I remember the statisticians, Jerry Cornfield and Fred Ederer in particular, felt strongly that these results were so extreme that we were not being true to what we told the patients in the beginning if we did not stop the study. We had told the patients that we were going to treat one eye and not the other, but if the treatment was shown to be effective we would treat the other eye. We had made a pact with these patients and it's interesting to me that it was the statisticians who were the most nervous about this pact between the patients than the clinicians. It's not that the clinicians weren't worried. They were also concerned about the patients, both those in the trial and those in the community. They wanted to be sure that they had the right answer. So the data monitoring committee debated at length and it wasn't clear at one point whether the statisticians were going to resign from the committee. I not sure if anyone ever knew how close we came to a major rift within the DSMC; it got pretty heated.

Mr. McManus: It would be in minutes from then?

Dr. Ferris: It should be, but the minutes often don't reflect the emotions

Mr. McManus: It would be interesting to dig out the ones from that time just to kind of document what was happening then.

Dr. Kupfer: See my only interaction was with Dinny and we almost came to blows. Was he sort of representing the feeling of the other statisticians?

Dr. Ferris: Dinny was originally on the side of continuing the trial, while the statisticians wanted to stop. When they agreed to postpone the decision to stop the first time the compromise was that if the 'p' value was less than .001 they would all agree to stop. And sure enough at the next meeting the p value was extreme. Because Dinny had worked through the compromises he was now committed to stopping the trial. However, those outside the committee had not heard the debate and the compromising necessary to reach consensus. I am sure he was representing this when he was talking to you. This data monitoring committee had been through an ordeal and had finally come to a consensus that was a relief for everybody. The idea that the study might not stop after all the consensus development was really a problem for him because they had come to this moral and ethical conclusion. Now, thrown into this ethical and scientific debate was the Policy Advisory Group. Here was a group of experts reviewing the DSMC decision. The data monitoring group would spend the entire day page by page going through the data and this group knew the data backwards and forward. The policy advisory group was a very senior group and I think they thought they had the authority to make the final decisions. They were not going to be a rubber stamp for this data monitoring committee and their discussions tended to be more theoretical than data based.

Mr. McManus: Of policy.

Dr. Ferris: Yes policy, but not necessarily data driven. As I remember it, the clinicians on that group too that felt that it was critically important to have an absolutely unequivocal result. After spending all this money we could not afford to have the community saying that we had not proven the treatment benefit to everybody's

satisfaction. As I remember it there was a mixed message. The data monitoring committee said "it's unethical to go a minute longer" and the policy advisory group is said "we're not sure that you can stop yet and convince everybody that this money was well spent". wasn't a part of that discussion when you and Dinny almost came to blows, but I heard about it from both sides afterward. I remember Fred Ederer doing what I thought at the time was a pretty good analysis to convince the policy advisory group that the study should stop.

Dr. Kupfer: Fred didn't tell them to do that.

Dr. Ferris: Well, I know, maybe you did.

Dr. Kupfer: Absolutely. I called Fred and I said look Fred there is only one way that I can come to a conclusion that's going to satisfy everyone. That you assumed that the treatment group starts going sour just like the non-treatment group and that the non-treatment group begins to have the same rates of response and good vision as the treatment group. What's the pay off?

Dr. Ferris: That was an interesting analysis. In this analysis, the untreated curve went from double the treated rate of vision loss to half its original slope, while the treated slope suddenly doubled. The interesting part was where the two curves met. As I remember it they met after about 10 years…

Dr. Kupfer: Twenty years, yes. The difference was so great initially that if they had a 20 year head start…

Dr. Ferris: And at that time this group of patients had about a 10 year 50% survival based on data that had been recently published. So, even if disaster were to strike they'd be way better off treated than untreated.

Dr. Kupfer: Well, that solved my problem.

Dr. Ferris: I think everybody was happy after that.

Dr. Kupfer: I think there's a lesson that comes through and that is that the entire structure of clinical trials was developed by statisticians not clinicians.

Dr. Ferris: Right.

Dr. Kupfer: And the clinicians had an awful need to run very, very fast to catch up.

Dr. Ferris: For sure.

Dr. Kupfer: And I think this was a good example.

Dr. Ferris: For sure.

Dr. Kupfer: It was very important.

Mr. McManus: That's right.

Dr. Kupfer: Okay, well that clears that up and I think that that has been very helpful and I did want to make that point.

Mr. McManus: How about this two-step progression and the three step progression. We talked a little about regular _____ but I mean that was pretty fancy stuff. I mean those end points were then the basis and I don't know Carl if you want to mention this or not but they were kind of a prototype for progression in other trials outside of diabetes right?

Dr. Kupfer: Well that was the stimulus for your ETDRS.

Mr. McManus: That's called macular degeneration.

Dr. Ferris: Sure, now we've spent a decade developing a fundus photograph grading scale that can be used as a surrogate outcome for progression of macular degeneration. This scale was submitted and was just accepted for publication. It is a nine step scale for progression of AMD. Surrogates for progression of diabetic retinopathy were especially important because photocoagulation preserved visual acuity and prevented blindness making these functional outcomes impractical for clinical trials.

Mr. McManus: Well even a new treatment for diabetes, like diet. I mean, that's only how you take control.

Dr. Ferris: So the development of a severity scale for diabetic retinopathy directly benefited future clinical trials for persons with diabetes. We were able demonstrate to the FDA the link between progression on the diabetic retinopathy scale and loss of visual function, making it a usable surrogate for clinical trials.

Mr. McManus: Do you think there ever could have been a type-controlled study without that?

Dr. Ferris: Well, I can say…

Mr. McManus: I mean that may be an overstatement. You can say what you think.

Dr. Ferris: Well, by far the most potent analysis to show that treatment effect was the retinopathy progression phase.

Mr. McManus: But it wasn't…

Dr. Kupfer: You're talking about entering the NIDDK?

Dr. Ferris: Yes.

Dr. Kupfer: You didn't compromise on allowing that to be the end point. You wanted to see something in the kidney that was really going to start a new end point.

Dr. Ferris: There was a very interesting data monitoring committee discussion as to whether the DCCT should be stopped early based on the retinopathy data. We were in a position where the retinopathy outcome was absolutely clear-cut. There was a highly statistically significant difference between the tight control group and standard group in retinopathy progression defined as a three step change on the retinopathy progression scale. The original primary outcome had been the development of microaneurysms in eyes without microaneurysms at baseline. However, the DCCT investigators felt that this outcome was too far removed from visual function to be a credible outcome variable that would be convincing of a real treatment benefit Who cares if they get one micro-aneurism? So the investigators requested that the data monitoring committee should not stop the study prematurely based only on the development of microaneurysms. They did believe that a three step change on that diabetic retinopathy scale would be clinically important.

Dr. Kupfer: Would you want to discuss that the suggestion for early stopping in the Age-Releated Eye Disease Study? My recollection isn't very good, in fact I had the impression that at one point we would consider bringing in another data and safety monitoring committee. Is that correct or was I making that up?

Dr. Ferris: Early in the data review of the AREDS there was a controversy regarding possible increased risk of antioxidants for cardiovascular disease. About two years into the study there was an imbalance in cardiovascular events and particularly cardiovascular mortality.

Dr. Kupfer: And you had a committee to monitor that, right?

Dr. Ferris: Yes, the Data Monitoring Committee reviewed the data every six months. The finding of increased mortality in the antioxidant only group followed close on the heels of a serious controversy within our trial about beta carotene. Two National Cancer Institute trials of beta carotene in smokers and asbestos workers both showed an increase risk for lung cancer in the groups assigned to beta-carotene supplements. This was a surprise because observational studies had suggested that beta-carotene supplementation should reduce the risk of lung cancer but within the trials there was a statistically significantly increased risk in those populations. At the same time data was released from the Physician's Health Study. This was a study of 18,000 physicians followed for more than a decade and randomly assigned to placebo, aspirin supplementation or beta carotene in a factorial design. This study found no apparent increased risk from beta-carotene but also found no apparent benefit. It was unclear what the beta carotene risk was in nonsmokers, but we recommended that AREDS participants who smoked should stop the antioxidant part of the randomized trial. Just as we have finished dealing with the beta carotene controversy comes this apparent increased mortality in the antioxidant group. The data monitoring

committee rightly concluded that they could not be certain as to whether there was any increased cardiovascular risk from anti-oxidant formulation in AREDS that included beta carotene, vitamin C and vitamin E. The committee had preset guidelines for mortality with a p value of 0.1. The committee discussed whether this was a chance finding or whether it was real.

Dr. Kupfer: But wasn't there a separate group looking at mortality that really was a part of the DSMC? They were the ones who…

Dr. Ferris: The internists served as a subcommittee of the DSMC, and they were responsible for review of systemic side effects. The two internists were particularly worried about the finding. They were on the committee for that purpose and they were the ones who were most concerned. In this case the statisticians on the committee were concerned that the findings of increased risk in the antioxidant group were likely to be a chance finding. This was based in part because the "antioxidant-only" group was only one-fourth of the AREDS population. There were study groups that were also taking antioxidants and zinc. This group actually had decreased mortality compared with the placebo group. If you took all participants taking antioxidants and compared them with those not taking antioxidants, there difference in mortality. It was only in the "antioxidant only" group where there was this apparent increased risk. However, the committee felt that the possible increased risk should be reported to the NEI Director.

Mr. McManus: Janet Wittes was the DSMC chair and Curt Furberg was the medical monitor…

Dr. Ferris: And Curt had had a recent experience with apparent increased risk from a calcium channel blocker, which was causing concern within the cardiovascular community.

Dr. Kupfer: When you say "we" you don't mean the Eye Institute?

Dr. Ferris: No, "we" in general and particularly from the perspective of the Heart and Lung Institute. Curt had been the head of the Clinical Trials Branch at NHLBI. The DSMC felt the study should continue unchanged, but there was a vocal minority that said that we needed

to report this to the institute. We went further than that. We met with the FDA requesting a review of the mortality data. They did not feel that we had adequate information to suggest an increased cardiovascular risk and agreed with the DSMC majority that the trial should continue.

Mr. McManus: Was Wiley ex-officio on that?

Dr. Ferris: I don't think it was quite that formal.

Dr. Kupfer: Wiley was on the DSMC.

Dr. Ferris: Oh, was he ex-officio on the DSMC.

Mr. McManus: I think it's a very important point. Because this was more critical what happened than I thought because I stayed.

Dr. Ferris: The AREDS DSMC included an experiment of including representatives from both the company and the FDA on the data monitoring committee. It was an experiment to assess whether this would enhance the ability of the committee.

Mr. McManus: We had three trials. We had more mainstream people from outside, like Janet Wittes and Curt Furberg, and I don't know if there were some nutrition people or not, and all kinds…

Dr. Ferris: This was a nutritionist on the committee.

Mr. McManus: And then we had industry, and then we had FDA. And I think it was too much. We had been so successful that we thought we could handle anything. And one of the most important if not the most important was compromised…

Dr. Kupfer: Earlier you said that at the presentation in FDA, they did not believe there was an increased risk?

Dr. Ferris: Well, they thought we were being silly overly cautious…

Dr. Kupfer: I see…

Dr. Ferris: They were not impressed by the 0.13 p value.

Mr. McManus: Now I was thinking about that, now what happened on the vitamin A study again? But they were talking about much higher doses of vitamin A, right?

Dr. Ferris: It is interesting when epidemiologists go beyond their own data. In this case they were suggesting that vitamin E was dangerous. A meta-analysis of all studies of vitamin E had recently been reported at a medical meeting in New Orleans This potentially could have an impact upon the thousands of people in AREDS because they are 400 mg of vitamin E was part of the study formulation. This provided even another worry that there may be increased mortality.

Mr. McManus: So you had thousands of patients you followed for a long time…

Dr. Ferris: Yes our study had follow up of thousands of persons on vitamin E or placebo and we part of this meta-analysis. We carefully reviewed the data from this meta-analysis. We felt it was most appropriate to look at the 15,000 patients in the meta-analysis that were taking around 400 IUs of Vitamin E…

Mr. McManus: How many in yours?

Dr. Ferris: Just under five thousand.

Mr. McManus: That was pretty good numbers.

Dr. Ferris: In all the studies testing about 400 IU of Vitamin E there were about 15,000 patients. Among those followed in these trials there were 862 deaths in the placebo group and 860 in the vitamin E group. Now my view of that is that's about as close to no apparent risk as you can get.

Mr. McManus: And these are good randomized studies?

Dr. Ferris: Yes, and that's a lot of people. And to say there's harm from this level of Vitamin E seems beyond what's reasonable. This also has to be balanced with the eventual AREDS results demonstrating a benefit in reducing the risk of progression to advanced AMD. You have to do the risk-benefit analysis. However, and I agree with the authors of the overall meta-analysis when they conclude that if you're taking vitamin E because you

hope it is going to make you live longer, you're probably wasting your time and money. There may also be an increased risk from very high doses of Vitamin E. Interestingly, if you look at our long term follow up data there's a 14% decrease risk in mortality in the people who are taking the full AREDS formulation, compared with those assigned to placebo.

Dr. Kupfer: I'd like to just finish up on the AREDS. If you would—and this is another aspect of clinical trials. I know Dan Siegel was a dissenting voice.

Dr. Ferris: Dan and I had several debates regarding study publications starting with the ETDRS. He thought we should not report our ETDRS results at the American Academy of Ophthalmology meeting. He felt our conclusions were too clinical. He wanted to stick to the hypothesis testing. He felt the study should stick to the statistical study design. It should be written so that statisticians would consider it a well written paper. However, it also had to be read by ophthalmologists who are going to do this treatment, and they have to read it and think that it's also a good paper. My concern was that the intersection of papers thought as excellent from the statistician's perspective those though as excellent from retinal clinicians perspective might be very small. However, I agree with Dan that if you're going to make a mistake in one direction or another you want to make it on the science side and not on the clinical side. Eventually I think we found some middle ground but there were heated discussions getting there. Then the AREDS came and that argument could not be settled by consensus. There's a little background here which I think is important. When we started the trial you and I were both very skeptical that zinc or antioxidants would reduce the risk of AMD progression

Mr. McManus: Oh yeah, we had a field day with this one.

Dr. Ferris: We were looking for scientific rationale to justify whether we should do the clinical trial or not. I remember asking David Newsome if he could provide us with his photos so that we could have them graded in Wisconsin to independently assess treatment effect. If we

could send them to Wisconsin and have them independently graded that would provide additional evidence that zinc should be studied. However, I was told that Dr. Newsome had lost the pictures when he moved to New Orleans. So we had little evidence that zinc was an effective treatment and Dr. Siegel was very much against doing this trial. I think in his heart he felt that zinc supplementation was dangerous and I think he still believes that regardless of any data. He recommended the NEI not do AREDS. I remember talking to you about the rationale for AREDS. If one was worried that the treatment toxic the only way to show it was within the trial. There was also an issue of zinc dose. Our nutritional advisors had suggested that 80 mg of zinc was too high. However, we seemed to be trapped. If we studied a lower dose of zinc and didn't find a treatment effect, what would people have said? "You wasted millions of dollars and didn't even test the dose that was shown to be effective in previous studies." So we were worried about the toxicity but recognized that this was truly a public health issue. If one was worried about toxicity, the only way you were going to be able to show it was to do the trial. You could never show it without the trial and hundreds of thousands of persons were taking that dose of zinc in the population.

Mr. McManus: I remember that we had a large group of people, they came in and went all though it and all and they would say things like that, but they never said that we shouldn't do the trial. They were kind of interested.

Dr. Ferris: They said they were worried about this dose of zinc but they did not say we shouldn't do the trial.

Mr. McManus: They were a little worried about the vitamin A.

Dr. Ferris: And I think that we are still worried about the doses studied in AREDS. We are currently talking about doing a follow up study to assess the beta carotene and zinc dose within a study of lutein and Omega-3 fatty acids. We could include formulations with lowered zinc and no beta carotene so that we can finally look at whether there is any obvious

difference in treatment effects at lower doses. However, within AREDS the DSMC all agreed that there was a clear treatment benefit of the formulation we studied.

Mr. McManus: All these really high-power people who babysat you the whole way through.

Dr. Ferris: They were all agreed. There wasn't one who thought that we hadn't showed a clear-cut benefit of the supplements. But Wiley, who was on the committee, at the end of that last meeting came up to me and said you know you have a failed trial, you know you didn't meet your .01 goal. The only analysis that was slightly over a 0.01 p-value was the analysis that combined the early drusen group with the high risk group. Well, it's interesting that he took this position, because he knew that the only reason we had included the small drusen group was to see if there was a group for whom benefit could not be demonstrated and who might not need to take supplements if supplements were shown to be effective in higher risk groups. When we modeled the original study we thought that perhaps 1% of the early drusen group might progress to advanced AMD each year. As it turned out the risk was much lower, with fewer than 1% progressing after 5 years.

Dr. Kupfer: Risk in terms of natural…

Dr. Ferris: Developing advanced AMD.

Mr. McManus: Was there any involvement in progression to higher risk groups in this early drusen group?

Dr. Ferris: Going into advanced AMD was ½% in five years.

Mr. McManus: Little drusen became big drusen and you're saying that that didn't happen?

Dr. Ferris: No, that did happen.

Mr. McManus: Oh, it did happen.

Dr. Ferris: Some participants who had early drusen at baseline developed large drusen during the study and supplements did not slow that progression. What rarely happened was progression to advanced AMD. Out of the thousand participants in that group, we had

only 12 that developed advanced AMD over the course of the trial. Putting this group into the statistical analysis of treated verses untreated lowered the overall event rate because one is adding 1000 participants that essentially had no events. When you include them in the analysis I believe that the p value was .02. When you just looked at the high-risk group for whom you were recommending treatment, the p-value was less than .01. And what Wiley was hanging his hat on was that overall group with a p-value of 0.02. Interestingly he was not interested in adjusting for confounding risk factors such as gender, age, smoking etc. These factors only had relative risks of less than 2, while the relative risk for the high risk vs. the early drusen group was over 30. Adjusting for factors with relative risks that large seem appropriate. We suggested that if one thought it was inappropriate to delete the early drusen group at the very least one should adjust the analysis for this confounding factor. In the end, including the early drusen group in the treated study created some controversy in the analyses, but I think was very important for our final study recommendations. Because we included this early group and could demonstrate that they had both a very low progression rated to advanced AMD and no apparent benefit from taking supplements, we were able to recommend that they probably need not take the supplements. This meant that we were only recommending supplements for about 8 million people in the United States and that the additional 47 million persons over age 55 in the US did not need to take the supplements. This is a significant recommendation that we could not have made if we hadn't studied the early group. Dan was unconvinced and from my perspective he had a no hypothesis robust to all data. He thought that supplements were not effective before the trial started and he wanted to believe he was right notwithstanding all data. So he was adamant enough about it that he eventually wrote a letter to the editor in *Archives of Ophthalmology*. We were able to write a response to his letter and I think Dan was disappointed that he didn't get much traction in the ophthalmology community from his letter. Because of this I

think he decided he was going to take it one step further. If he couldn't convince the physicians he would convince the patients themselves so he wrote a letter to the editor of the *Washington Post*.

Mr. McManus: It is important that you had full DSMC review of this issue.

Dr. Ferris: We even had a review of the issue with added biostatistical expertise and clinical trials expertise. We talked to Dave DeMets and he even agreed to come. But it turned out that he never needed to come but he agreed—he didn't want to but you twisted his arm.

Dr. Ferris: Well, there is one other thing that I think was important about the 70's at NIH that I will bemoan for two minutes with some editorial comment. In those days, here on the campus, we had tremendous expertise in methodology and clinical research. They have largely left the NIH campus now. Most of the epidemiology groups have moved off campus and most of the methodologists have left NIH. I went to a meeting of the Society for Clinical Trials meeting several years ago. At that meeting only about 4% of the papers presented were by NIH people. There remain very important methodology issues in clinical trials, but the expertise to address these issues has largely left NIH.

End of Transcript