Adrian Hernandez: Hey, this is Adrian Hernandez and welcome to the NIH Collaboratory Grand Rounds podcast. We're here to give you some extra time with our speaker and ask them the tough and interesting questions you want to hear most. If you haven't already, we hope you'll watch the full Grand Rounds webinar recording to learn more. All of our Grand Rounds content can be found at rethinkingclinicaltrials.org. Thanks for joining.

Hi, this is Adrian Hernandez, one of the moderators for Collaboratory Grand Rounds. And today we're here with Susan Ellenberg, who is going to describe what she recently presented on data safety monitoring board for trials in the COVID-19 era, and talking about some of the lessons learned and the challenges. So Susan, thanks for doing this with us.

Susan Ellenberg: Well, you're welcome. I'm glad to be here with you.

Adrian Hernandez: So just to give a little historical perspective, how many years have you been on. DSMBs? And how many DSMBs have you been on, do you think?

Susan Ellenberg: Well, I haven't counted. I'm sure there are people who have been on more than I have. My first experience with DSMBs was when I headed the biostatistics group at NIAID in the early days of the AIDS treatment trials. And we had a DSMB overseeing the trials of the AIDS clinical trials group and the community group that was doing trials. And it fell to me to organize that meeting, and that was really my first experience. So that started back in the late 1980s. And since then, I've been on numerous DSMBs or data monitoring committees, as they are known in industry, both for government trials and for industry trials. And also, I've of course reported to a number of DSMBs since I've been at Penn as part of the collaborative projects that I've been involved with as the senior statistician.

Adrian Hernandez: Well, Susan, that's an interesting start, talking about the HIV as it was emerging. There was a lot of unknowns, what the disease was, what potential therapeutics were, and a lot of public pressure in terms of what to do back [inaudible 00:02:24]. What was that like when you all were starting this effort to treat HIV?

Susan Ellenberg: Well, it was interesting. The very first meeting I attended was pretty chaotic. There was an amazing DSMB with terrific people, clinicians, bioethicists, and statisticians. The statisticians on that committee were Tom Fleming and Dave DeMets, known to many of you. Butch Tsiatis had also initially been on that committee. He had to leave when Harvard took over the role of being the statistical center for the AIDS clinical trials group. And the first meeting that I went to, the industry representative was in the room for all the discussion, and the head of the FDA antiviral group was there for the whole discussion. The only person who wasn't permitted to be in the room was the principal investigator for the trial, who sat outside the door in case we had any questions. And I was really quite taken aback by a lot of the discussion.

I remember the industry person in there seemed ready to say, "Oh, we have enough information to stop this trial." Or, "What are you talking about? Intention to treat analysis. We're not doing that." So after the meeting was finished and as people were packing up, I went to talk to the DSMB members and I said, "Are you happy with the way this is set up?" Because even though I didn't have a lot of experience, this just didn't seem right. And they all said uniformly, "No. Please fix this." So we it was an interesting time trying to work out how to have the DSMB look at the interim data by themselves, which was going to be terribly resistant. At that time in the late 1980s, there was very little data monitoring committee work in industry. I think the cardiovascular trials may have been some exception, but for the most part, companies just reviewed the interim data themselves. There wasn't a DSMB.

So they weren't used to the idea that they couldn't have access to the interim data. And when we tried to make this change, there was a lot of pushback. We ended up having several meetings about it. And the FDA was very resistant too. They felt they needed to be on the cutting edge. They needed to know everything that was going on. So they were prepared to move quickly if a trial was stopped early. Nobody wanted to be in a position of looking like they were delaying the availability of an effective treatment. Remember, this was a time when AIDS was a death sentence and the only treatment out there was AZT, which people were recognizing wasn't that great.

So we came up with this idea of having two sessions, an open session where we would have the industry person there and the FDA people there, and the principal investigator there. And we would just talk about how the trial was going, the company and the NIH program people were there as well. So the DSMB could be informed about other things that were going on that might be relevant to the trial and we could talk about any issues in the trial progress or quality. And then they would all leave and the DSMB would reflect on the comparative data. So the comparative data would only be seen in this closed session as opposed to the open session. And like I said, there were still some resistance from industry for a while, but that worked very well. The NIH leadership said, "Okay. You can do it this way." And this became pretty much the standard for now how data monitoring committees are run with an open session with participation by the people actually doing the trial and sponsoring it, and then a closed session where the comparative data are reviewed.

Adrian Hernandez: Wow. That is quite remarkable. Never imagined. DMCs that didn't have open and closed sessions. So certainly a beneficiary of all your groundbreaking work back then. Now fast-forward to where we are now. What was it like last year when you all were called to serve? What was the circumstance?

Susan Ellenberg: Well, I guess this started back last summer. I think many of us were surprised and pleased that the Phase III trials, the large field trials were able to begin as quickly as they were. And we were all holding our breath to see what these trials would show. One of the trials that we were reviewing... We did not review

the Pfizer trial, but the Pfizer trial and the Moderna trial were using a new technology that had never been used for vaccines. And so we really didn't know what to expect from that. The trials were going to be starting at different points in time. And because several of them were going to be running simultaneously, we understood we were going to be kept very busy. And we were going to be reviewing the data for every trial monthly, with other ad hoc meetings as scheduled.

So basically, every week we were having a meeting with one trial group or the other. And as I said in my presentation, one of the challenges was that each trial had a different data management and statistical center. So it wasn't the uniformity of reporting that I was used to from other times where I had been on a DSMB for a trial network where that DSMB was reviewing multiple trials from that network. But those were all done by a single statistical center. So there was a uniformity of presentation. So that was a challenge. And I think when the Moderna trial reached its point of interim analysis, which was amazingly quickly because there was no problem in accruing people to these trials, we were all astounded but to see how strong the evidence was and how high the vaccine efficacy was. So it's been a very challenging and intense but very gratifying experience.

Adrian Hernandez: Wow. You mentioned a few challenges. What are going to be kind of key lessons learned from the past year for DSMBs that can apply for either future pandemics or future important public health problems?

Susan Ellenberg: Well, one thing I think we would all like to have seen is a single group reporting to us. I think that was probably impossible in this case because of the rapidity with which the data are coming in and the complexity of these trials there were various things that had to be reviewed. There was laboratory data coming in. There were case report forms describing the experience of people coming in for an illness visit who might've had COVID. There was an adjudication committee looking at everything. And I don't know whether a single group could really have handled that for all the multiple trials that we were doing. But to the extent that it could be possible, that would really have made our job easier to have a consistent presentation in the same group that we were talking to at each meeting.

Adrian Hernandez: Great. And then, I guess if you had to do to it all over again, would you keep the same kind of structure where you have a single DSMB across these different trials? Or would you have individual DSMBs for the different trials?

Susan Ellenberg: No, I think it was very valuable to have a single DSMB because if a safety issue emerged in one trial, we could very quickly look to see whether we were seeing the same things in the other trials. And even though each of these vaccines was slightly different, still, they're all working to protect against the same virus. And so there would be some plausibility for if something was a problem with one, it might be a problem with the other. So that was useful.

And we had seen this in the past on rare occasions where data monitoring committees might share information with each other when a safety issue emerged that wasn't clear whether it was real or just one fluky thing that happens. If there's another similar trial ongoing to be able to say, "Are you seeing the same thing?" You don't want to stop a trial for harm if it's a fluke. But on the other hand, if it's not a fluke, it could be very worrisome. So I think it is helpful to have a single DSMB, and I would not recommend against that in this kind of a situation, however burdensome it is for those of us serving.

Adrian Hernandez: Great. Well, Susan, thanks for chatting about your experience on the DSMB for COVID-19 vaccine trials and sharing about what transpired and the challenges and also lessons learned.

Susan Ellenberg: You're very welcome.

Adrian Hernandez: And thanks everyone for joining us on this podcast. Please join us for our next podcast as we continue to highlight interesting and informative changes in the research world.

Thanks for joining today's NIH Collaboratory Grand Rounds podcast. Let us know what you think by rating this interview on our website. And we hope to see you again on our next Grand Rounds, Fridays at 1:00 PM Eastern Time.