that well-designed studies should be able to document that outcome is improved and at the same time that survival isn't affected in a substantial way.

We have been trying to do those studies for the last decade and hopefully, with new agents, we will be able to do them better.

DR. POLLACK: One of the challenges is that when you are making tradeoffs like that, the determinations are kind of arbitrary, how much of a dropoff in survival we, as physicians, might be willing to tolerate, 10 percent, 5 percent, how much of an increase in IQ or some other measure of quality of life do we want to see 1 standard deviation, a half a standard deviation, and those are things that we can build into the trial, but that the tougher things are that for many families, they make decisions based on not concrete measures like that.

Some families want to see the best possible chance of survival and are willing to accept morbidity. On the flip side, there are

families who are not willing to accept morbidity and are more comfortable accepting a lower chance of survival.

Those are I think the things that is very hard to build into a study, so you wind up in designing these studies coming up with concrete targets that may not be necessarily acceptable to everybody.

DR. ARMSTRONG: I think that we need to be incredibly careful in this discussion and really push to a different setting a lot of discussion about the topic we are treading around.

The degree of impairment that many of our childhood brain tumor patients experience is on a magnitude of scale significantly less than many people who fit into the developmental disabilities arena from genetic conditions.

This discussion in an open setting of Down syndrome, of children with other neurologic impairments, who are working on independent living, who are receiving disability services, would be blasphemy at its worst, because they would look at

this and say how can you be talking about trading off survival for X.

I think this is a very important question to deal with because we talk about this in the cancer arena. But there is a whole world of the ethics of developmental disability that we need to put this in the context of. Perhaps one of our issues is making the connection to the disability world in a more effective way, not defined by brain tumors and cancer, but by the functional disabilities and challenges that are there.

So, I think it is a topic that is really worth discussing. But when I put on my hat as the director of a developmental disabilities center where issues of involvement in community setting and independent living, and everything else are issues, if I had that university shut down for the last month because the president didn't recognize the culture of deafness or didn't fit the culture of deafness that that particular group did, and that way of thinking is not something that may fit with the way that we think in oncology. But, out

in the world, it is a significant issue. I think we need to tread very carefully.

DR. LINK: Not all the trials are going to be related to cognitive disability, I mean some of the toxicities. We do this all the time in trying to eliminate radiation to prevent secondary malignancy in Hodgkin's disease knowing that you are going to have a higher recurrence rate, so it is not like this tradeoff has never been done before.

Some of it may be ototoxicity, things which are not necessarily threatening to your ability to live a relatively normal quality of life.

DR. PACKER: I agree completely with what Dr. Armstrong said, coming as a child neurologist and seeing the same kind of children.

It is very difficult for me to evaluate the ability to cure someone versus the effect of the treatment in the long term. You try to balance it out and you try to be objective, but the other problem in trial design is that sometimes this is

what the study is and you have got to live with it.

The one thing that I did want to comment on was the comment that we always are designing our studies with both of these things in mind. The reality is these studies are usually powered for one thing or the other, and that is why some things is a primary objective and by some things a secondary objective.

We power our studies for the primary objective where we might need 10 times as many children to evaluate that secondary objective, and we are fooling ourselves really if we say that we are really doing that.

We are writing it down because it's important and someone is going to review our study and not let it get approved unless we write it in. But, in reality, we are not going to hit that measure.

That, to me, is a critical thing as we go on study design, and not try to fool ourselves of what we are trying to do.

DR. LINK: Other comments?

DR. KIERAN: The comment that Danny raised. I guess the one difference is that in the developmental neurology clinics that you speak of, of inborn errors and those kinds of issues, the difference is we caused the toxicities, we caused the damage, and therefore it really is a discussion of what we are willing to cause in order to try and prevent, and that's a little bit different than taking what you were born with and dealing with it accordingly, and although you are right, there are many patients that are equally or worse off than brain tumor patients. It doesn't diminish how affected they are.

So, I think the conversation that comes back between the family, the physician, and therefore the studies that we have for them, has to take some of those variables into account.

DR. SWISHER: I think I would agree with that, that although a lot of the children that I see do have developmental disabilities or learning challenges, it is different as a population of parents to deal with.

One is that I signed the consent that condemned her to that life, and it is more like traumatic brain injuries where a lot of the children remember what it was like before, so the social and psychological impact is much more different than being born and that is the only thing you have ever known.

DR. LINK: Those are obviously very important comments. I think also the problem is that different families evaluate those tradeoffs very differently.

I dealt with it just actually a week ago talking about trying to enter a patient on a study that eliminated radiation, and the family, who were physicians, said that survival was paramount and they weren't worried about what was going to happen 15 years later, they were worried about the here and now.

You would think that that would be an unsophisticated sort of response except that they were physicians, so that they were very aware, I mean you could talk in medical terms, so it was

surprising to me. So, different value systems have to come into play.

Craig.

MR. LUSTIG: I think that what we are really trying to do is not necessarily--we are trying to give people greater choices than they have now ultimately, and to my mind, that is very important to families.

So, if you will, it is more of a consumer driven way of thinking about this, which is to not necessarily make the judgment about what is right for them, but to give them options and right now they don't have very many, and if they had more, then, they can make that judgment.

DR. PACKER: I can also point out that there was a statement made that we are doing these studies that are trying to both improve the quality of life and overall survival.

We are entering a series of studies in brain tumors that are not going to improve anyone's quality of life if they are a survivor. We are reintroducing methotrexate. We are reintroducing

radiation where we have given up on it in specific areas.

So, it is an interesting thought that we are doing this balance as a community, and we have had improved survivals through the FDA and through CTEP, we know that with the increased survival, there is no chance that there is going to be improved quality of life, that the only thing we can hope for is that we haven't hurt quality of life.

We have accepted that as a community because we have opened those studies, so I think we just have to be honest with ourselves of what we are doing and maybe we are not listening to the advocates appropriately, maybe we are not listening to the survivors, and I don't know how to balance out a discussion with a family who has a very damaged child versus a discussion 24 hours earlier of a child who is about to die.

It's a hard balance. The last thing about giving options. Options are wonderful but we also have to give guidance to those options, so it isn't

quite as easy as saying okay, we will have panel A and panel B, you decide whether you want to risk a 20 percent loss of survival versus a 20 percent loss of IQ.

I don't think it is that easy, and I don't think we design studies to have those things that dichotomized.

DR. LINK: So, the answer to the question is we would like to do them but we don't think we can do them well, when we are not sure even what the parameters are that we would design the studies around.

DR. WEISS: I think regardless the discussion around those topics have raised some very good points. When we went into this we realized that there weren't specific yes and no answers. It was really more to get a discussion, get some things on the table, considerations for studies, for outcomes, for considerations.

We heard a lot even about making sure that we include the advocacy community in these discussions. So, I think we have had a lot of

useful input and just so you don't go home thinking that you haven't done your job, you have.

DR. LINK: We stand adjourned then.

DR. WEISS: Again, thank everybody for coming and participating today.

[Whereupon, at 3:35 p.m., the proceedings were adjourned.]

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