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P R O C E E D I N G S

INTRODUCTION

DR. RIDER: Good morning. We would like you to take your seats so we can get started.

On behalf of Dr. Janet Woodcock, the Director of the Center for Drugs, Dr. Kent Johnson, and members of the Tri-Center Rheumatology Working Group, I would like to welcome everyone to the FDA Workshop on Juvenile Rheumatoid Arthritis. Today's meeting is in follow-up to the Rheumatoid Arthritis Workshop held on March 27, 1996, which was a public forum for the Rheumatology Working Group to receive comments and suggestions on its draft rheumatoid arthritis guidance document.

Dr. Woodcock asked that I extend her apologies for not being here today. She has been called to the Hill to testify on FDA reform and she will try to stop in later in the day.

Before we begin, there are a few administrative matters to be taken care of. There is a break room in which we have coffee and soda set up, which is in the Gallery Room, located across the hall. The phones and restrooms are just outside in the lobby area of the first floor. If you have not previously registered, please do so at the break.

The purpose of today's meeting is to address

issues in the document which are specific to juvenile rheumatoid arthritis. We will be meeting all in day in sessions to obtain comments and explore if consensus can be reached on a number of issues that require further discussion for JRA because of differences in disease pathogenesis and expression from adult rheumatoid arthritis.

These issues include claims and labeling for anti-rheumatic therapy in JRA, which will be discussed in this morning's sessions, as well as appropriate designs and approaches regarding the conduct of JRA clinical trials and issues pertaining to the science of drug development in JRA, which will be raised in this afternoon's sessions.

The draft RA guidance document, however, addresses additional topics not specifically discussed in today's workshop, including preclinical studies, pharmacokinetics, pharmacodynamic strategies, and special considerations on the development of biological products and devices.

After today's meeting, all topics in the draft RA guidance document, including those discussed today, may be commented on by submitting written comments to the workshop docket. The workshop docket, No. 96D-0067 will remain open for comment until August 30. All comments will be reviewed and considered by members of the Rheumatology Working Group in drafting the next version of the guidance document.

Our Rheumatology Working Group members are here today and we would like to acknowledge their efforts by having them stand. Thank you.

Our goal for this morning's sessions is to carefully consider whether the structure of candidate labeling claims and endpoints for adult rheumatoid arthritis can be applied at this time to the development of new agents for juvenile rheumatoid arthritis. The claims which have been structured for the development of new therapy for adult RA include reduction in clinical signs and symptoms, improvement in functional ability or quality of live, prevention of structural damage, and achievement of remission. If these claims are appropriate for JRA development, are there outcome measures unique to JRA that would be needed to support these claims?

Additional ethical concerns underlie the conduct of research studies and clinical trials in children and we are pleased to be joined by Dr. Sanford Leikin, an expert in the ethics of childhood chronic illnesses, and welcome the interspersion of additional thoughts on this subject throughout the day.

Our day is organized into formal presentations on each topic, followed by time for open discussion of the presented issues. During these periods, first priority for

comments has been given to a panel of critical commentators, a group of leading clinical pediatric rheumatologists who may help us gain longer-term perspective on these issues. Thereafter, we are open for open discussion from members on the panel, members of the Rheumatology Working Group, and participants in the audience. When stepping up to the microphone, we ask that you identify yourself and your affiliation.

Because of our very full schedule today, we will give signals when we are falling behind and need to move forward.

Without further delay, I would like to begin the morning with presentations on the structure of clinical signs and symptoms claims for JRA. Our first speaker is Dr. Edward Giannini, who will speak on the development of a core set for improvement for all JRA subsets.

CANDIDATE LABELING CLAIMS AND ENDPOINTS (I-V)

I. SIGNS AND SYMPTOMS

CORE SET FOR IMPROVEMENT FOR ALL SUBSETS OF JRA

DR. GIANNINI: Lisa, thanks very much. Let me take this opportunity on behalf of myself and the other pediatric rheumatologists in the audience to thank the FDA for going to the time and effort and expense of putting this

symposium together. It comes at a time when many people feel that our subspecialty is about to undergo a poposis [ph.]. Whether or not our subspecialty undergoes that, it is clear that some of our patients' T-cells are not doing it, at least the pathogenic ones, so we are going to have to find some way to carry on.

About five years ago, we had a committee that undertook the task of rewriting the FDA guidelines for the study of anti-rheumatic and anti-inflammatory drugs in children. The last ones were published in 1988 and we wanted to bring them up to speed.

I believe that you have the executive summary of that document that was published in A&R last year. It's by myself, Dan Lovell, and Bonnie Hepburn. It is what it says it is, and that is it is a draft and we submitted it to A&R in hopes that we would have some discussion about it in the form of letters to the editor and so forth, and to my knowledge, we didn't get any, which means that it is either perfect or it's beyond all hope or nobody cares. I don't know which of those three it is.

In that document, we clearly say that we're not quite sure what we should use for the assessment of response, determining if a patient has, in fact, improved or not, but we did have a project ongoing at that time, or we

were starting one, I should say. What I want to present this morning, then, is the results of that project.

Through the help of the Arthritis Foundation's Clinical Science Grant, we were able to carry on this project and it is recently completed and the proceedings have been given to the panel members, the entire proceeding, which looks like this. It's this blue book that summarizes the proceedings from a conference that we just had in Pavia, Italy, and I'll discuss why we met in Italy in a little bit, or do I even have to? It was Cincinnati or Italy--

[Laughter.]

DR. GIANNINI: Anyway, I have chosen some pages out of that book to put in the handout that the rest of you have, and so you can follow along in your handouts as much as you wish.

Can I have the first overhead, please? I'm going to blast through this pretty quick to get to the meet. Lisa added about five questions for me after I had my time slot, so if I go a little over, I apologize.

To give credit where credit is due, as I said, this was done with an Arthritis Foundation Clinical Science Grant, but we certainly did have to have some other pharmaceutical sponsors, as well. Can I have the next overhead?

I've given credit on that cover page, also, to the OMERACT effort that some of you may be familiar with, and if a lot of this looks familiar to those of you that have been following OMERACT, it should, because I have copied quite a bit of it, although I tried to improve on the methodology where I could and avoid some of their mistakes, but I certainly want to acknowledge their effort.

The identified problems of having multiple endpoints and so forth in JRA clinical trials is shown on this particular slide, and I am not going to belabor them. Certainly, it does cause a variety of different problems and they are shown here, so if I could have the next slide, please.

Why does this present a problem? The lack of standardization can lead to inefficient trials, to increased chance of statistical error, possible reporting bias, and probably the worst, two multiple interpretations of the data. So if you have some variables that change by what is considered a statistically and clinically significant amount and others do not, you're pretty much left in a lurch as to interpreting whether or not the drug was any good or not. And then finally, inability to compare multiple therapies using meta-analytic techniques. No one is going to study all these new drugs in one trial and so we have to have

methods for cross-comparing trials. The next slide, please?

So the goals of the project that were outlined in the Arthritis Foundation grant are this, and that is to develop and implement a core set of endpoints that can be used in all clinical trials of therapeutic agents for treating JA, and let me use the more generic term JA instead of getting into the JRA argument.

To describe the amount of change in each variable that is considered clinically important, you use the entire core set to classify each patient as either improved or not improved. Now, let me make the point right off the bat that this is simply a core set, in that you would be free to measure any other variable that you wish, but yet the core set would always be measured, and further, you wouldn't necessarily have to make this core set be your primary outcome.

So then the long-term goals, to increase the efficiency of clinical trials such that fewer kids need to be enrolled into these experimental protocols, and finally to standardize and clarify methods for the reporting and analysis of these trials. The next slide, please?

The little page numbers you can see on the handouts is what corresponds in the full proceedings of the program that some of you have. So this would be page 16 in

the blue book.

So what did we do? About three years ago, then, we started by forming a committee, and this was made up of members of the Pediatric Section of the ACR, the Rheumatology Section of the American Academy of Pediatrics, members that were participating in the OMERACT project, and then, finally, academic and private practice pediatric rheumatologists.

We did the least expensive thing we could and that is we sent out a preconference questionnaire--we are leading up to a conference here in a moment--but we sent out a questionnaire and said, you, as a doctor, when you look at a kid, how do you determine at which endpoints do you like in figuring out and helping you figure out if that patient improved or not?

These were the responses, ranked in order, as we got them. You can see the MD global of disease activity was on the top, followed by functional ability, the parent-patient assessment of disease activity, the active joint count, swollen joint count, swollen joint score, the overall severity score, the SED rate.

We took those, then, and went to a couple of data banks, in particular, one that has been collected over the last 15 years by our group called the Pediatric Rheumatology

Collaborative Study Group. We had 551 kids in this data bank that had all been studied under identical protocols. They were all DMARD studies. We looked in this data bank to see what the validity, sensitivity to change, redundancy, and so forth of these different variables was in this data bank.

We also used the literature. We certainly weren't the only ones that had been doing clinical trials in kids for the last 20 years or so, so we looked in the literature, trying to come up with some estimates of these validity characteristics of these outcome variables, not combined into an index at this point but just the individual variables, to see if, for instance, they correlated with anything that we thought was important or they correlated with x-ray changes or whatever.

Then we held a conference two years ago now in Marco Island, Florida, and we had a group of us there. Many of the folks at this table were there. We presented the data from our initial studies at the time of that conference and then we used nominal group technique, which is a consensus forming technique. It combines opinion driven by data to come up to a consensus about what variables should be in a core set. As a warmup for judging from pieces of paper what patients improved and what didn't improve by

using this core set, we also looked at patient profiles and tried to determine if those patients had improved by a clinically important amount. The next slide, please?

So this is what we came up with. This was our preliminary core set, physicians global, parent assessment of overall well-being on a 10 or 15 centimeter visual analog scale. We didn't think it was important to distinguish between 10 and 15. I don't think we think it's important now. But anyway, we didn't specify.

Functional disability, we didn't specify the exact instrument because, at that time, they were still all doing validity testing and under development, for the first part. The number of joints with active arthritis, the number of joints with limited range of motion, and then finally an acute phase reacting got thrown in there and we included the SED rate.

We still had a lot of work to do, then, after the Marco Island conference. We needed, for instance, a broader consensus about this preliminary course set, not only from U.S. rheumatologists but also international. The first, the Marco Island conference, was limited to individuals in North America.

We needed to know if practitioners are willing to use the core set variables as a single entity to classify

patients as either improved or not improved. We needed an estimate of how many variables in the core set would have to improve and by how much before practitioners would classify the patient as improved. We needed to know how many variables practitioners are willing to ignore if they worsen and by how much and still classify the patient as improved.

So again, we did the cheapest thing, the only thing that we could afford to do, really, and we conducted a questionnaire, a much more broad questionnaire survey now, and I won't belabor how we got the sample, but there it is.

So if I could have the next slide, let me show you the results of that. For those of you who have the complete program, it shows you a copy of the entire questionnaire, but it's not important. I can tell you pretty much what the questions were.

It presented them with much of the data that was presented at the Marco Island conference and said we do, in fact, have a preliminary core set. You don't have to choose them. Here's a whole smorgasbord of things to choose from, and if you had your pick, what would you choose? Here is our sample size here from Europe and from North America and these are ranked. They were asked to rank their variables, and you can see that they pretty much were similar. There were some differences between Europe and North America, but

pretty much they came out with the same ones.

So if you combine the ranks from the two samples, we come up with an n of 140 and you can see, lo and behold, we came up, fortunately, with the same core set. Not only that, there was a nice break between the top six and then the next one down here, duration of inactivity, stiffness. So that gave us a little bit more confidence in the fact that we were at least on the right track with this preliminary group of variables. If I could have the next slide, please?

There are some other questions on there. Question B, and for those of you who don't have the questionnaire, we simply said, all right, that is fine. These are the variables. If you want to call that improved, how much does it have to change from baseline? The number to remember here is 30 percent. This is the combined, meaning both of the samples combined, this is a combined median and you can see that it's 30 percent. Here is the combined mode over here, a little bit higher than that.

C was a question about the number of variables that improved in order to call the patient improved. So people said, I would need to see improvement in at least three of those variables by this amount before I would call that patient clinically significantly improved. The number

of variables that you could ignore if they worsened was two. The maximum deterioration in those that you could ignore, this was the median--excuse me. This is the mean, 25 percent. The mean is 30 percent, and the index to dichotomized patients as improved or not improved.

What this question stated was, would you be willing to use some core set, some group of variables and put it into a single index so that you could dichotomously say whether or not this patient has improved or not improved? A hundred-and-twenty-four of the 140 said that they would be willing to do that. The next slide, please?

The issue of redundancy, then, multicollinearity of the variables, and, of course, that had to be investigated with more varied data sets other than the large one that I have already talked about, and again, I don't think you're interested, but we had some other data sets that we were able to get these statistics from.

Let me show you the results of those. Simple correlation coefficients showed that, in fact, as you might expect, a lot of these variables did show multicollinearity. In other words, they were correlated with one another. These are straightforward r values and you can see that they're not extremely high, but yet there is some correlation between them.

Now, in general, statisticians think that an r value of 0.7 or higher is generally considered to be strong evidence of multicollinearity, so I was a little bit encouraged by this in that even though they are related--you know, if they weren't related at all, you would kind of worry about it--but they weren't overly related.

Further, for some of the variables, we could calculate r values for changes, for the deltas. So, for instance, if we looked at the change in the number of active joints versus the change in the SED rate, we came up with an r value for the delta of 0.16. So that was at least a look-see to see how much redundancy there were, because if these were all 1.0, then there's no need to have more than one variable because you're measuring the same thing. The next slide, please?

Then we needed to develop definitions of improvement to be tested to see how sensitive, specific, ease of use, and credible they were. This is just one page of definitions. For instance, the first one up here, two of 86 improved by at least--I can't quite read that--20 percent and none worse. There's 240 of these different scenarios. Notice also that we did not include all mathematical possibilities because we knew we would be wasting people's time.

So, for instance, here, two of any six improved by at least 20 percent. No more than two worse was the maximum we took it to, because we know from our survey that if a patient demonstrated worsening in three of them, no one was going to call that patient improved. So these were the definitions of improvement, then, that we were going to test. The next slide, please?

Further, these definitions of improvement needed to be tested for their discriminating power using existing clinical trial data sets, and those were very, very limited. The point here is that if a definition of improvement shows good sensitivity and all the rest of it but doesn't discriminate well between active agent and placebo in an actual clinical trial, then it's probably not the best pick. The next slide, please.

So the goals, then, of the conference in Pavia that we just had in May were these: To decide upon a preliminary definition of improvement using the core set of outcome variables, using the combination of statistical and consensus forming techniques. This is the process we used to get there. We have rated each of 72 patient profiles as improved or not improved, again using nominal group technique, and then we calculated these performance characteristics, as they're called, the sensitivity and

specificity and so forth, using the physician's decision as to whether or not the patient was improved as a gold standard.

Observe the ability of the remaining definitions of improvement to discriminate between active agent and placebo, using existing trial data. Then we used nominal group technique again to decide upon which of the remaining definitions of improvement is easiest to use and most credible, in other words, had the highest phase validity. And then finally, we multiplied that phase validity score by the kappa value to obtain what we refer to as the final answer. And again, if you participated in the OMERACT project, it's very similar to what they did.

Here is an example of those patient profiles. These are actual patients, I should tell you. We didn't make these up. Here was, for instance, the MD assessment at baseline, at the end of the trial--actually, this was a clinical experience, not a clinical trial--the absolute change, and then the percent change. They were then, after silent evaluation, asked to score the patient as clinically importantly improved or not, and then for those that we didn't reach 80 percent consensus on, we had a discussion on those and then scored the patient again. The next slide, please?

This is what the final judgment of the patients looks like. We met in plenary session. Here's patients 1 through 24. Again, we had 72 of them. Some of them, we agreed at the 80 percent level that they had improved. Some of them had not improved. And others, we scored as uninterpretable. We couldn't decide if they had improved or not, and for reasons of this analysis of this method, we threw these patients out. So these were the ones that we were working with.

Again, this means that 80 percent of the practitioners in the audience agreed that this patient, for instance, had improved. This does not indicate the amount of improvement in the patient itself. The next slide, please?

So after day one, we got busy, after all these profiles were scored, and myself and my clinical fellow sat all night analyzing the data while everyone else went out to drink some Italian wine and we found nine definitions that met our preliminary screen in that they were at least 80 percent sensitive and 80 percent specific. So if you compare, if you look at this little two-by-two table up here, here is the number of patients that the doctor called improved and not improved and then the agreement with the particular definition. So there is the little two-by-two

table that we are going to do the chi square on, the p value, sensitivity, specificity, false positive rate, false negative rate, and the kappa statistic. So let's go to the next slide and I'll show you what those definitions are.

Excuse me. I'm sorry. This is the discriminate validity of those. Dan Lovell presented this part of the workshop. We took the best drug that we had trial data on. You know, sensitivity and specificity and sensitivity to change is really only a function of how good your drug is, and really, the drug that we got the best results with was 10 milligrams/meter/squared per week of methotrexate, and that's the data that we used, again, because discriminate ability is a function of how good your drug is. And we compared the percent of patients that got better by each of these definitions in the methotrexate group versus the placebo group.

Let me caution you that this data is very tenuous, and Dan stressed that in the workshop, too, because not all of the variables in the core set had been measured in these trials. So we had to derive some of them from regression analysis. Some of them had to be converted from a Likerglike scale [ph.] to a linear scale. For instance, the MD global assessment in the actual trial of methotrexate was scored much better, better, same, worse, much worse, but we

had to extrapolate that down to a linear scale, which isn't the best. So the data here are highly derived and Dan cautioned the group about that when judging these particular statistics for their--these particular definitions for their discriminate validity. So let me have the next slide, then.

So the next thing, then, was for the practitioners to break into the group again and score each of these--excuse me. They were to choose five of these nine variables that met the preliminary screen of 80 percent sensitive and specific and score them for phase validity, with five being high and one being poor. These are the definitions, then, that we're working with, and you can refer back to those when you see the final result.

If I could have the next slide, then, this, then, is the final results of our Pavia conference. Definition 6A and 6B and 9A were the top vote getters. Here is the final score. I can't quite read it. I think it says 60, 42, and 35. You see there's a nice break here. These clearly were our best definitions.

If you look at 6A and 6B, they're very similar, and that was encouraging to us because if the highest one, the one with the highest score, would have been very different than the one with the second highest score, we would have worried about the process that we used. The

third highest one, 9A, if you take a look at that on that previous sheet, turns out to be very, very close to the Pollus criteria, and so we were encouraged by that, that, in fact, we were in a way validating in pediatric rheumatology the Pollus criteria used in adult rheumatology. So we were very encouraged that, in fact, these top three vote getters were extremely similar and that 9A was, in fact, or almost the Pollus criteria.

If I could have the next slide, the top vote getter, just as a reminder, was three of any six of the core set variables improved by at least 30 percent with no more than one of the remaining variables worsening by no more than 30 percent. That was our definition of improvement that we came up with.

If I could have the next slide, that brings me to the conclusion of my talk. Lisa asked me a few questions. Why not different core sets and definitions of improvement for the different onset types? I will tell you the real reason that we did it and that is, first off, when we started this project, we knew that the different onset types were undergoing change at that point, that there was going to be a new classification scheme, and we really didn't know how that was going to fall out. In fact, we still don't know.

Secondly, we didn't think that we could ask in a survey, and we had a limited amount of time and money to do this, think about the outcome variables of core set for systemics, for polys, and for Paucis.

Next, there was little evidence that the onset types influenced response. If I could have the next slide, and then we'll come back to this one. I want to show you some data here. Lisa asked me to look at this before the meeting.

This is the response by onset type on the first table up here, patients used for the consensus conference. And again, there was 72 of these. It turns out that there were 15 Paucis--these are onsets now, not course--23 polys, and 34 systemics. Now, you wouldn't expect that. This is, of course, not a valid cross-sectioning of all the JRA patients that you see. Systemics are over-represented. But again, this was a clinic sample, not a randomized trial.

So you can see the percentage of the patients that were improved here, scored as improved during our consensus conference, and those that were uninterpretable, and I argue with you that there is not much difference. Actually, the next one has a chi square. I don't think that there's much statistical significance, anyway, in terms of the frequency of improvement, of a favorable response among the onset

types.

Now, the middle chart here uses our Collaborative Study Group core data bank. In here is 504, not the 551 that I showed you before, because we only included the efficacy subset. So here, we had 151 Paucis, 245 polys, and 180 systemics, a huge sample now, and you can see--here's a chi square with two degrees previous. We'll get a two-by-three table. The chi square was four and the p value was 0.13.

Finally, some of these patients received placebo. These were all the patients in the efficacy subset. We say, well, that's fine. Let's just look at those that receive active agent and it comes out to 307, and still there's no difference here, that the chi square with two degrees freedom was 3.2 and the p value was 0.2.

So if we could go back to that other slide now, from our data base, anyway, there's little evidence that the onset type influenced response in terms of the articular and functional outcomes. I'm not talking about pericarditis or iridocyclitis or anything like that. I'm talking about articular outcome and function, which is probably what we're most interested in anyway in these trials, unless, of course, we design a trial to look at the effect of steroids and naprosyn, for instance, on iridocyclitis.

The next point was that we attempted in our proceedings at Marco Island and in our surveys and in Pavia to keep in the front of everyone's mind that the core set should be designed to be robust enough for all of the onset types, no matter how the onset types fell out.

We focused on features common to all onset types, arthritis and functional disability. So maybe we're downstream. You know, whatever the etiologic agent is, it's systemic or Pauci and maybe there's different T-cell receptors involved, whatever, maybe by the time they get into our trials, we're downstream enough with the inflammation that, in fact, the mechanism for producing the arthritis is pretty much the same at that point. I don't know, but that's the theory that we're working with.

My final point is this. If one begins splitting the disease, that geneticists won't allow you to stop the splitting at the broad phenotypes of the disease. For instance, each of the subtypes can be broken down further even clinically, so people like David Glass aren't going to let you stop at splitting poly from Pauci. They'll say, I can show you that there is a difference in outcome among the early onset Paucis versus the late onset Paucis.

Further, you can break down even those by genetics. So, for instance, let's take polys. What if you

wanted to split them into--our group into those who were DR4 positive versus DR4 negative? Well, that's fine. Am I confusing disease risk with outcome? I'm not sure, because for many of them that have been shown to produce disease risk, it's also been shown that they can, in fact, influence outcome.

But look at DR4. Using the new terminology now, just DR4, we can split into, using new terminology, DR beta 1 0401 through 0408 and only a few of those splits are arthritogenic and perhaps influence outcome, and the same is true for DR5, which we know to be important in certain subtypes of JRA.

My point is, we have no earthly idea at present what other genes may influence outcome. Look at the IDDM experience, an experience very close to my heart. If you look at the article last year in Nature, they found in the whole genome search, using affected sib pairs methodology, they found 18 chromosomal regions across the genome that influence disease susceptibility and perhaps outcome. There were only 11 of those that were very strongly linked, but still, JRA shows less family trait than does IDDM and there is probably even more genes involved.

Further, if we include multiple ethnic groups in our sample, the problem becomes worse, due to differing

effects of the same gene in different populations. In other words, it relates to gene combinations.

So you've heard the scenario that if you would combine a DR4 and a DR1, then your prognosis is much worse than it is if you just have DR1. So the whole thing is a mess at this point, and I guess I am arguing that maybe our kids or grandkids will worry more about this problem than we should.

Lisa, there were a couple of other questions that you asked me, if I can do it in 60 seconds. Plans to change the core set over time? I think we'll have to let everybody else do the leg work, so if someone has an IL-2 receptor antagonist or something, they're going to have to provide most of the information before we'll consider putting it into the core set.

How will organized meetings like this in the future--I'm not quite sure. My overall point is, this core set and definition of improvement are not in stone. It simply gives you something to throw stones at and we would be glad to change it later on if someone shows us that they have a better index for measuring change than we have now, or for describing improvement.

I think the rest of them, I'll leave for the discussion.

DR. RIDER: Okay. Thank you.

DR. GIANNINI: Are we going to wait for questions?

DR. RIDER: Yes. We will wait for questions and we will move on to our next speaker. We are ready to consider whether additional or alternative outcome measures are needed for other subsets, first beginning with Pauciarticular JRA by Dr. Carol Lindsley.

ARE ADDITIONAL/ALTERNATIVE OUTCOME MEASURES NEEDED FOR PAUCIARTICULAR JRA

DR. LINDSLEY: I attempted to answer the question with regards to the usefulness of additional variables relevant to Pauciarticular JRA. This is the preliminary core set that Ed just went through, and I approached this by thinking about whether we needed additional outcome variables for Pauciarticular disease.

In this disease, there are very few joints involved and there's limited variability or range in your parameters and power to deal with that. We know from many of our studies that there is a high placebo response, and perhaps some of the sensitivity of the variables may contribute to that. Just from a common sense standpoint, we know that Pauciarticular disease is a very regional disease and it makes sense that some of the more general parameters may not be as applicable to that particular type of disease.

So I looked at my own clinical practice and the type of parameters and data that I had collected to monitor my patients and came up with some additional variables that I thought were at least worth considering. One of these--the first three, actually, relate to functional ability, and I'll show you some data relevant to that in a minute.

The first one relates to knees. Since many Pauciarticular children have knee involvement at some time or another, knee function becomes a critical parameter. Looking at knee range of motion with a weight-bearing type of focus is what happens with a deep knee bend, or in a young child, picking up a toy.

Another one is the ability to weight bear on stairs in a reciprocating fashion. If a child has instability on one side or another, they will always lead with that side and the lack of reciprocity indicates some ongoing instability or discomfort.

Gait abnormalities, these vary whether it is a limb or increased circumduction in the gait or persistent toeing out or an asymmetric toeing out can be indicative of ongoing problems. General parameters, such as a.m. stiffness.

Longer-term variables, such as a limb asymmetry,

where there is muscle atrophy or leg length discrepancy are very helpful in assessing the long-term effect of localized disease.

Then looking at our active joint score, as well, the consideration perhaps of not just limitation of motion or a global active joint count but looking, specifically in children that have only one or two joints, looking at the presence of a fusion, of pain on motion and limitation of motion, in other words, giving a larger power for that active joint score.

And then some functioning screen. As far as physical activity in school, this can be helpful in picking up problems. Then in children that have eye involvement, perhaps vision would be an outcome. And there's one other one that I want to comment on later that is not on here which is the pain VAS.

To consider this, I just took within the last week or two a look at Pauciarticulars that I had been actively following in my clinic and had seen at least four times in the last 24 months, and you can see the demographics here. Almost all of these were ANA positive. I wanted to look, and this was really not a definitive study but I wanted to just look and compare the two sets of variables, looking at which ones that I felt had shown, first of all, some

fluctuation over their disease course and which ones were helpful in monitoring these children.

You can see with regards to the core set of values that in these 13 patients, most of them did show some variability, and, indeed, I perceived them to be helpful. The striking one that was not was the functional ability screen, and in these kids, we had used the childhood HAQ and also in some of the patients just an ADL type of evaluation.

You can see with the additional variables that I had nine children that had significant knee involvement and that all of those knee flexion with some sort of weight bearing was helpful, and again, you can see out of the 13 how many of those different variables showed some variability and were felt to be helpful.

Also, from focusing, then, on the functional ability screen, looking at some of our other studies, a couple of childhood compliance studies that we've done, and again, where we had used the HAQ, just to show that in Pauciarticulars, the mean score, as I think we all know, is very, very low.

With regards to correlations of disease measures with the HAQ, again in this compliance study, you can see then, particularly in the polyarticular disease, there is good correlation with global improvement, with joint count,

with stiffness, but--and particularly in those three in Pauci, there is not good correlation.

In a separate study, in a pain study that we did involving 74 children, again, looking at just morning stiffness, this was a reminder that stiffness, even with Paucis, can be of significant duration, and, in fact, the mean was actually higher than it was in the other two groups. So even though we may be talking about one or two joints, morning stiffness in this particular study was a helpful measure.

Then another measure that we have used a lot is the pain VAS, using a ten sonometer scale. Again, in the Pauciarticular population, the pain mean was in the same range as it was with more generalized disease. So some of these parameters, such as pain and stiffness, are probably as useful in Paucis as they are in other subgroups.

We had also done another study looking at--these are the Pearson correlations for parental rating lists and this is about a ten-year-old study, but we showed that there was good correlation, again, just by parental ratings, from morning stiffness and activity limitation, as well as, to a lesser degree, to pain.

So I think that there is good indication that some of these other parameters have some specific usefulness in

Pauciarticular disease where other variables, particularly functional screens, may not be as helpful.

So in answering Lisa's question, I guess my plea would be that when we are doing studies with Pauciarticular disease, that we consider, at least for the functional ability screen, some of the additional skill parameters that relate to function, particular of lower extremity joints, and that we also keep in mind that some of the more diffuse parameters, such as morning stiffness and pain, can be very useful in children with limited disease. Thank you.

DR. RIDER: Thank you.

We'd like to continue with considering whether additional or alternative outcome measures are needed for systemic onset juvenile rheumatoid arthritis by Dr. Earl Silverman.

ARE ADDITIONAL/ALTERNATIVE OUTCOME MEASURES

NEEDED FOR SYSTEMIC ONSET JRA

DR. SILVERMAN: Thank you. Well, the easy answer would be, yes, there would be, and I'll try to explain why I think that, not that the core set, as pointed out by Ed, shouldn't be included, but maybe that's not the primary outcome, and I know Ed said this doesn't have to be, and I concur completely with him that the core data, the core set is very good and measures many things but may not for systemic JRA or JA be the primary outcome. I'll review basically why by going to clinical features, laboratory, HLA, with the caveat that I've already mentioned very quickly, both that response and some of the differences, and importantly, some of the outcome differences.

It's pretty--to this audience, I don't have to review this very much, but it's obvious that the clinical features of systemic JRA/JA differ from other ones. If you take out arthritis for a moment, these are the five features that I felt really distinguish it. Obviously, by definition, you have to have fever.

So if you don't have fever, you can't have systemic JA, and I would argue that without fever as a variable in outcome, are we really going to get after treating this disease? Lymphadenopathy, hepatosplenomegaly,

serositis, and lastly, to differ from what we just heard, a lack of uveitis in this disease. So it differs from the other major types and, obviously, if you want to divide it even more into four subtypes, clinically, that the only feature, in fact, it has in common--two features, one, that it occurs in childhood; two, there is arthritis. I'll try to show you why, in fact, maybe that's not even that important in the long-term outcome.

This slide shows data from--actually, data from Dr. Cassidy--showing outcome in patients with oligoarthritis, and if you look at the differences between erosions, hip involvement, knee involvement, C-spine involvement, that although these patients had oligoarthritis or Pauci arthritis, the erosions, the involvement completely differs and if we feel erosion, C-spine, ankylosis are important, hip involvement, we all know, is important to outcome, I would argue we must measure different things if we are going to alter the course, if the primary outcome is actually altering course and actually making a difference rather than looking for improvement, that the disease differ.

Again, this again shows the difference between patients with polyarthritis on x-ray changes, again showing that there were significant changes occurred more frequently

at one year if there's active systemic disease, and again, one should have to differ patients with active systemic disease versus those who no longer have active disease.

The laboratory features in the core set ESR was discussed. ESR may, in fact, not be the primary feature that may differentiate and predict outcome. Studies by Schneider and Lang had shown that thrombocytosis at six months, in fact, was what really predicted best long-term x-ray changes as a measure of outcome. If the platelet count was over 600,000, there's a higher chance of going on to get significant x-ray damage.

Obviously, elevated leukocytosis, anemia, and one can put in other ones. The point of this slide really is to say the measurement of a single laboratory feature, ESI, may not be the best predictor, that because it works well in polyarthritis and maybe not so well in Pauci, it may not be the best indicator of active systemic disease.

HLA associations, I'll go over quickly and they'll be addressed later. Obviously, they differ. But the other thing I want to emphasize on this that is not on the slide is maybe it's not HLA. Maybe we should consider the difference of the so-called tri-molecular complex that alluded to T-cell receptor, HLA, but as important antigen. If these diseases are the same, why does one have fever and

why does one look like a viral-type infection? Maybe the antigens differ. So again, to lump them may not be clever, at least for outcome.

And not finally, but we're now into response to therapy and remittive agents, and this is just again a--some data from Toronto. Remittive agents were used in systemics, and you see a certain virus. But the things I want to point out are if patients were polycyclic or persistent arthritis, most of them were on prednisone, at least at some time in their therapy, again, differentiating from the other subtypes.

DMARDs are used frequently, obviously, methotrexate, obviously, and at biased interims the high percentages of intravenous immunoglobulin.

Also, the response to therapy differs. All the audience is aware of the adverse reactions to Gold. In my opinion, it's contraindicated in this disease. Adverse reactions to sulfasalazine. These are drugs used in trials in other forms of arthritis. How can we then use them in this disease if it's to measure the same outcomes?

The hepatitis we see with non-steroidals and the question still unanswered, potentially in my mind, does methotrexate work in act of the systemic, not for polyarthritis?

So the data to date suggests that maybe drugs that we have now do not work as well, they have a different side effect profile, and therefore we do need different measure outcomes and to treat these patients separately.

Finally, the suggestion of maybe what should be added not in place of the core variables but added to the core variables. Fever, my personal bias would be, would be the number one outcome variable, and that's based on the experience of most people in the room that if one can control the fever and the systemic features, one can control the disease. Potentially other systemic features--are we measuring the right laboratory parameters? Functional outcome, it is measured in the core data base--variables, excuse me, and, of course, joint activity. The last two certainly are covered in the core variables and the top three potentially are not. Thank you.

DR. RIDER: Thank you, Earl.

We would like to turn now to discussion, beginning with critical commentary by our group of commentators, Dr. Balu Athreya, James Cassidy, Ross Petty, and Patience White. Dr. Athreya?

CRITICAL RESPONSE

DR. ATHREYA: I believe it's Ed about having a core set, but I think we're also saying maybe we have to add

other sorts of criteria for other subsets. I just tried to put the core set and tried to see how well I think it'll work. It's just purely a clinical feeling, and when I put Pauci, systemic, poly, and then put all these six of those the way he suggested in a core set, as already it's been pointed out, I have concerns about the core set answering properly for the Pauci group, as you can see, number of active joints, and there was only one or two. How are you going to say?

Functional scale, there is a supporting point for that. The constants as the conference spoke, which Ed shared with me, I was looking at it. Actually, I was trying to look at all those patients where there are less than five joints and try to see how well it did. Actually, it didn't do too well even that 72 patients it was given. One of the interesting things was, and all of those numbers were high because the doctors said it was wonderful but the patients didn't rate it that way.

Then I was wondering about the number of joints with limited range of motion, since the active joints have been also as part of the definition, whether there is any question of redundancy in that, and I am surprised to see ESR, and, of course, we know it may not work too well.

Then I just wondered whether for at least some of

these subsets--we already heard from Dr. Silverman, too, about the systemic type--so if we, at least for some of the subsets, Pauci and systemic, if you can remove the limitation on motion--actually, I changed my mind since I prepared this one--we need to keep the functional scale. Remove the limitation of motion but then add some extra articular features, such as some of the ideas from Dr. Lindsley and Dr. Silverman.

One last point, I did what you already heard about. I think Dr. White may want to comment on that. I was just trying to compare the pediatric measure with the adult ACR measure. You can see MD global is the same, PT global is the same, and the number of active joints in the pediatric, whereas their tender and swollen joint count--I think Dr. Patience White may want to comment on it--functional is the same and then this number of joints with a limited range of motion, I do have concerns about that. SED rate is the same. And then you see how, in adults, two mandatory, and then three of five with 20 percent improvement, and in the pediatric, you have three of six and nothing worsening. Thank you.

DR. JOHNSON: If the other commentators have comments, you can either go up to the podium or do it right from the table there, whichever is easier.

DR. CASSIDY: Why don't I just stand right here. Is that all right?

DR. JOHNSON: Yes. You don't even have to stand. You can sit.

DR. CASSIDY: I think this is a very interesting discussion, and to Dr. Lindsley's suggestion, I would add that in Pauciarticular disease, joint circumference, I think, can be a valid measurement of improvement, along with her emphasis along with increasing leg length discrepancy.

Then with Dr. Silverman, I had independently also put down the fact that I think our core set in this disease has got to evaluate laboratory measures--thrombocytosis, hemoglobin, white count, and then systemic features such as fever and rash, which are really unique to systemic disease and, for the most part, not seen in the other ones.

Then in a note to Ed before the meeting, I think that we are perhaps ignoring the most powerful evaluation that we can perform in these studies, and that is instead of depending upon outcome measurement as a single slice of time, if we would define outcome as a trend with at least two sequential measurements all going in the same direction, say at six and eight months, something like that.

Ed, in thinking about your comments and the way the previous pediatric studies were done, I wonder if some

of the data may not actually be misleading at this point in view of what has just been said at this meeting. For instance, in the Paucis, perhaps some of those children actually improved more than our data would indicate simply because the parameters that were being used may not have been sensitive enough in a child with a single joint, involved the knee, and no systemic features to show that that improvement had taken place.

Then in the systemics, perhaps some of those patients actually lacked improvement, again, because although parameters were measured, they were not selected out for outcome, and we could mention the ones that have been underlined here, the hemoglobin level, the thrombocytosis, and the white count.

Then finally, I'd just like to make an independent comment that hasn't come up yet at the meeting and that is in many of my systemic patients, I become quite discouraged that they're ever going to improve. I don't know whether that is an HLA-related event or not. But if a study is loaded with those systemic patients, then power of a DMARD is going to be grossly underestimated in relationship to the Paucis and the polys, particularly in that study. In fact, I'd like to know if others here feel that our systemic patients end up being the real struggles in our clinics.

DR. JOHNSON: Dr. Petty?

DR. PETTY: Thank you. The core set of criteria, it seems to me, have been derived from adult criteria used for adult rheumatoid arthritis, which parallel in pediatrics is polyarticular onset JRA. I think that imprint is both a good one and a problematic one, because I think there's vastly more heterogeneity within the JRA group than there is within the adult RA group.

I think, furthermore, that we should attempt to be clear about classification. I even hate to bring up the topic, but I think Ed has already mentioned it. If we are looking at children other than ACR defined JRA patients, we introduce even more heterogeneity, such as the spondylorathropades group [ph.], wherein, again, for Pauciarticular children, the criteria would be, I think, primarily meaningless because of the fact that so many other manifestations of their disease dominate their clinical pictures.

Pauciarticular JRA, to my experience, is a disease of knees and ankles, but almost never of small joints and very seldom of upper extremity joints. I think that experience is borne out by others in the literature, as well. For that reason, I think, as Carol has indicated, we ought to recognize that knees are the focus joints in these

children and, therefore, any functional assessment which fails to accommodate that fact will miss the point. We won't find change, because there won't be change. So a functional test that doesn't somehow recognize that fact will fail to demonstrate change of any agent we use.

Similarly, the ESR, which I have not yet discarded, unlike Dan Lovell, is not much use to you in an oligoarticular child. It's usually normal. So to use it as a core variable in this situation seems to me to again invite failure to demonstrate change rather than accentuation of change.

With respect to systemic disease, I think we're confronted with similar but different problems, one of which is that the systemic features of the disease which lead to improvements in global assessment by physician and patient or parent aren't reflected by changes, for example, in the joint count, and this is compounded by the fact that there are time elements involved in this.

The systemic manifestations of this disease, fever, rash, all the serious signs and so on, are usually worse at the beginning and usually the joint disease in those bad kids gets worse over time so that we have a sort of split between the severity of the systemic features and the severity of the articular features so that it would

depend in time as to where you measured which, as to which variable would be useful to you, a global assessment or a joint count.

I agree in principle with virtually all of the comments which have been made. I think in certain circumstances, they're all entirely valid. I think for example, that the leg lengthening quality issue which Carol mentioned is a very important outcome measurement if you happen to have unilateral knee involvement. If you have bilateral knee involvement, it's entirely unimportant, so it won't help you.

Similarly, with uveitis, if you have had uveitis, then your corrected vision is very important as an outcome variable. If you haven't had uveitis, then it seems meaningless to try to measure it.

With systemic onset disease, I agree with Ed. I think the fever is the outcome measurement which influences the global assessments early and it should be included at least in some phase as an outcome variable. Thank you.

DR. WHITE: I have the pleasure of being at the end of all these astute folks and, obviously, agree with what people are saying.

I have a few questions about the core data set. I guess the first question is, when you look at the adult and

pediatric, how do you define an active joint? I wonder what people's assumptions were, because even when I filled out those forms, I wondered how people were looking at it. Was it tenderness, was it swelling, and so forth, and you can see the difference in the core data sets because people were looking at swelling. They were trying to define what activity was.

Also a comment, in Lisa's write-up of the Pavia conference, I'm equally concerned about limited range of motion because we all know that contractures occur early in kids and they don't necessarily improve because they don't have that memory to say, "I'd like to walk without a limp." The arthritis could be gone and you're left with a kid with limited mobility.

So I'm worried about that. I'm just putting my worries on the table about that core data set and would have to define it a little bit better, which was implied on the limited mobility in a comment made at the Pavia conference about maybe it should be--this is an issue about physical therapy and so forth. So I think that those are the comments I want to add on the core data set.

The other, I think, in general, we're dealing with different diseases. We all are having a hard time deciding why they're different, but they're different. I think

everybody would say they're different, that Pauci is different from poly, and then we can go on and on about breaking them up. I think that it's very hard to get a core set for different diseases and I think we're going to have to face that and decide, okay, we're either going to look at onset, we're going to look at course.

We just have to decide what you're looking at, and I think that's what the company has to decide. In other words, are we aiming for a drug for arthritis? Are we aiming for a drug with systemic features? I think that would help us, because if you're looking at a drug that might potentially affect systemic features, then limited mobility is a non-issue. Or if you're looking at outcome morbidity in Pauci, iritis is the issue.

So I guess I'm sitting here saying that I don't think it can be one set. I think that's what all of us are saying, and I think you have to define what you think you want to do with your drug or with whatever trial, and then hopefully as a group here, we can say there are some things that we would add if you happened to look at this particular group. I think that's what we're beginning to do, and I would agree with iritis and some of the comments that are made about Pauci and certainly with systemics featuring fever and platelet count become a key issue, as has been

shown multiple times before.

That is the end of my comments. Thank you.

DR. RIDER: We'd like to take comments from the rest of the panelists, as well as the audience, at this time.

GENERAL DISCUSSION

DR. KATONA: Lisa, one of the interesting things that we have been listening to all these core values and we have not heard any pediatric unique features in it. One of the things we all know, that the polyarticulars and especially the systemic onset children will have severe growth degradation. One of the proposals that I would like to have, at least for those to consider to put in, at least changing the role of the VAS or defining it, but that could be a pediatric unique feature. Thank you.

DR. WHITE: The issue is time here, too. In other words, over six months, kids have a variability of growth. So I guess the other obvious issue always here is how long do you say is optimal, and if you're going to look at a year only, then I think all these other issues become important. If you're looking at a six week, six month, then those kinds of differences amongst kids and growth would be hard. I agree with you.

DR. POZNANSKI: I was going to ask Ed, in the

various criteria that you used, did you find a difference between the very young and the older children? In other words, the very young behave much more differently in terms of ability to talk about symptoms than the older teenagers. I wonder whether that would have made a difference in sensitivity and specificity in these.

DR. GIANNINI: We didn't look at that specifically. I can tell you, the mean age of the kids that are in these trials is about nine and a half. When we developed the core set, we kept telling people to keep that in mind, the cognitive ability of these children. That's one reason, for instance, the pain isn't in there and tenderness that's in the adult core set, is that we were worried about the cognitive ability of the majority of the patients that we enroll in these trials. That's another reason why we couldn't use the adults as it was. But yes, true, our kids are very young. Nine and a half is the average age in the core data bank.

Can I answer a couple of other questions? The definition that we used for active joints was the one that Earl in 1976 put forward and then Jim verified in 1986, and that is swelling, or if no swelling is present, then limitation of motion with either heat, pain, or tenderness, and the swelling can't be due to bony enlargement with

currently burned-out inflammation.

DR. WHITE: Right. Then it's redundant. You're asking limited mobility, right? In other words, your activity and your limited mobility are very close, because it's a criteria, for one, right? In other words--

DR. GIANNINI: Right, although--

DR. WHITE: And I'm worried about that as a core set in itself. That is what I was just saying.

DR. GIANNINI: I understand. You saw the r values between swelling and limited range of motion are fairly high, but I also can tell you that the majority of joints that are considered active are active because they're swollen, not because they're limited with limited range of motion with one of those other parameters.

Again, with the addition of extra articular features, I think it's been said a couple of different ways, and they're correct, and that is that if we're interested in iridocyclitis, then that's how we develop our eligibility criteria. But certainly, if you were going to use any extra articular features in--if you were to consider adding to the core set, don't forget, then, you've got to include that in your eligibility criteria for the trial and that greatly limits your ability to enroll patients.

Another thing that we emphasize during all these

proceedings is to keep in mind that the best-designed study in the world with no patients in it is a failure. We tried to keep our heads buried in reality here as to what types of manifestations of disease that patients were most likely to have. That gets back to sensitivity to change and not include something that very, very few patients might have.

Let me turn it over while I think of something.

DR. WALLACE: Just a few comments. I would like to urge everyone to consider the idea that maybe what we should be looking at is disease course. I doubt that we're going to be looking at kids in the first six months of disease. If we are, fabulous. Then we'll do really early onset and I'd be all in favor of that. But beyond that, I think it makes most sense to look at the disease course and I think systemics are really a very different kettle of fish than are the vast majority of polys, Paucis, et cetera.

The other thing that I worry about is along the lines of reliability is using the global assessments in the teenage years or even starting at age 11, because those kids desperately want to be normal. Those kids desperately don't want a thing wrong with them and they're just totally--I think, quite unreliable.

Now, one could screen those and take out the ones that you know are unreliable, but I really think we need to

go for where the gold is, and I think looking at activity of joints makes most sense. Then for those that have extra articular features, looking at that, as well.

DR. LINDSLEY: I just want to comment, Carol, with regards to adolescents. In some of our pain studies, we found very good correlation between the pain VAS, the adolescents did, and the parameters of active disease, as opposed to--and maybe you could say that that's part of global assessment, but looking specifically at pain, there was good correlation there.

DR. WALLACE: Yes. No, I think probably if you asked specifically about pain, but as a part of--

DR. LINDSLEY: Right.

DR. WALLACE: Is your disease active? Of course, it's not active.

DR. LINDSLEY: Right.

DR. ATHREYA: Commenting on this sequential and the timed evaluation, how long is long enough is the question, because, at least for the experience, I think that methotrexate is wonderful as long as you give it and some kids are on it because each time you try to stop--I have not been successful in getting the kids off methotrexate once they're on it. What are some of the consequences of that in a child, as he grows up, and how long is long enough?

DR. GIANNINI: I think the answer to that is what you know biologically about your drug. I mean, if it's an NSAID versus a DMARD versus a biologic. If you are going to advertise that this thing is going to produce efficacy within six months, well, then your time frame probably should be no less than that, versus three months for some NSAID. So I think that's part of the protocol rather than the outcome.

DR. ATHREYA: It will come up again later when we talk about the definition of improvement in active disease, remission--

DR. JOHNSON: In the adult world, we dealt with this same issue and there's been actually a heritage, I guess, of non-steroidal trials going a few months. In the end, it's a little bit arbitrary, but we did kind of make a call at about a three-month point with regards to signs and symptoms in general.

But for something that was of a greater clinical import, whether it be remission or arresting the x-rays or whatever, we thought that the disease and the concept of the therapeutic goal that you're after should drive that decision to be longer and we just decided arbitrarily on a year there. Now, whether those dynamics should apply to JRA is another issue.

Could I just ask Ed a couple of technical questions? When the PSSRG, or the Soviet and U.S. collaborative studies were done and so on and a global was asked of a patient or a parent or a doctor, were they asked to look at the entire organism, incorporating things like fever and iritis and so on?

DR. GIANNINI: Yes. That was--the question was very simply stated and that is in comparison to how--the overall patient's status at baseline, how are you doing now? It was much better, better--

DR. JOHNSON: But in the OA world of adults, for instance, the phrase tended to have been something like, with all respects to the OA of your knee, how are you doing, or something like that, some phrase that kind of focused you in on that joint and not what was going on with the rest of the body. But evidently, that was not the case with these--

DR. GIANNINI: No. That is right. The way it is--in the core set, the way we fashioned the question is we stole it from the CHAQ, and that is, in consideration of all the ways your arthritis affects you, how are you all doing?

DR. JOHNSON: All the ways your arthritis affects you?

DR. GIANNINI: Yes.

DR. JOHNSON: So somebody might--

DR. GIANNINI: No. Excuse me. I am sorry. It says disease.

DR. JOHNSON: Disease?

DR. GIANNINI: Yes.

DR. JOHNSON: So, I mean, conceivably, you could now take your Pavia algorithm and you can take the data on MD globals and on patient-parent globals and see how frequently they match per subset, and if there is a lot of mismatches in the systemics or the Paucis, and then--

DR. GIANNINI: Kent, I think that was on that slide.

DR. JOHNSON: Was it, though? I thought this was just an improvement or not improvement.

DR. GIANNINI: The last slide. I am sorry. This was just the physicians' global, is what this was based on.

DR. JOHNSON: Wait a minute. So this is how frequently the algorithm that you derive, the core set that you derive, matches the physician global?

DR. GIANNINI: No. This is simply how many patients--this is asking a different question. How many patients in the subsets, in the various subsets of the disease, were improved or not improved? We could not really use the algorithm, see, because we did not ask all of those items in those Soviet trials. We tried to get to that with

the slide that Dan showed, but as I said, those are highly derived because we had to convert scales from physicians' global being much better, better, same, worse, much worse, down to a continuous scale, and we really didn't measure functional ability in those, either. We derived it through regression analysis.

DR. JOHNSON: Let's try this, then. In your group of 72 patients that you discussed--

DR. GIANNINI: Okay.

DR. JOHNSON: When they were given the preliminary information about those patients, were they given non-articular information or were they just given--

DR. GIANNINI: No. Just the information on those cards.

DR. JOHNSON: So we don't really have a data base that we could truly test. I mean, it seems like the major reservation here is perhaps kind of myopically looking at it as a concern that the physician global is not being addressed. The physician sees a platelet count of 700,000 and he worries about it, but we can't really test that question, I guess, with the data we have.

DR. GIANNINI: Yes. I agree. I mean, there are not existing data sets right now that allow us to validate our core set. That is one of the goals for the future, as

we stated, is the prospective validation of this core set. It is just something for us--or definition of improvement, I should say. It is just something for us to beat on, someplace to start.

DR. JOHNSON: Let me just make one other comment. I mean, I think that whole collaborative effort was incredibly valuable because we are going to need to have some straw man out there. There are other ways of enrolling patients of various types, including various subtypes, and doing a clinical trial and doing an outcome that everybody would agree is credible, and you would just simply set up a test of success that bears on the patient's subtype.

For instance, you could say that an oligo patient would be deemed successful if he passed the Pavia test and if he did not have worsening in his iritis, if he had it, or if his platelet count came--I mean, you could put all these caveats actually into your clinical protocol. You do not have to have them as a--they do not have to be in the core set to be usable in a clinical trial. I guess that is an obvious point, but should be made, I think.

Then if you are going to do a trial with JRA as a totality, you will probably want to stratify so you get at least a decent number of each of the subtypes in the trial.

DR. GIANNINI: That is the trouble, getting the

decent number. You have to keep this buried in reality here, Kent.

DR. JOHNSON: But you had almost balanced subtypes, didn't you? What were your proportions in the--

DR. GIANNINI: Yes, but I'm not sure that each one of those would meet a statistical sample size requirement. I mean, it's interesting that we broke them down for this purpose here, but if we were actually to do a power analysis on this, I am not sure we would have adequate numbers.

DR. JOHNSON: But if you had a trial of 120 patients that were just sequentially enrolled or something like that, what is the breakdown of the three subtypes as it stands now?

DR. GIANNINI: Again, it depends upon the protocol. If it's a methotrexate protocol, you can bet there's going to be a lot more polys in there, and if it's an NSAID protocol, probably a lot more Paucis, and a biologics protocol, I don't know.

DR. WHITE: I think it's the issue of, as Dr. Wallace brought up, of course versus onset is the key thing here, because when I was thinking about patients I put into trials, they may have had a Pauci onset but they truly had a poly course. I think that's a very important differential we have to sort of decide on, because I think that we're now

watching. Andersson Gare's article nicely pointed out the shift that occurs. Or, we're going to have to decide on a time again, and I don't want to get in this debate, but I think that is going to be very important in the group that you put in.

DR. JOHNSON: If you take a cross-section of JRA patients who are severe enough to be on methotrexate, how does it break down?

DR. WALLACE: Polys, polys, polys.

DR. WHITE: But they may have had a bunch that were Pauci onset. See, that's an issue.

DR. JOHNSON: Okay, but at that time.

DR. WHITE: Right.

DR. LOVELL: I think one of the things that has been overlooked here is the core set was designed and validated on a data base set with the expectation that they would be used in DMARD trials, so that this core set that Ed has talked about would be functional for DMARD trials or second-line agent trials and we wouldn't utilize this core set if we were going to do an NSAID study, for example.

As a consequence of that, when we looked at the various parameters, we took patients who had only been enrolled in DMARD trials. We did not use the study group data base from all the NSAID trials. So this core set

really isn't intended to be used for all JRA trials, such as short-duration NSAID trials, but really was designed to be used for the longer duration second-line studies.

With that in mind is how the limitation of motion parameter got put into the core set, because it was the single best item that distinguished between placebo and higher dose methotrexate in that study. So certainly, if you wanted to do an NSAID trial, you probably would not put that parameter in there.

But this core set is really intended to be used for DMARD trials, and when you do look at those patients, they are all polyarticular course, because when we thought about utilizing these drugs in our early trials, we were quite uncomfortable with the concept of using, say, methotrexate or oral gold, which at that time was considered an experimental agent if the patient only has one or two active joints, knowing that the outcome with those patients is really quite good with our more traditional measures.

So by kind of a selection process of those people who are designing the trials, it is going to be primarily polyarticular course patients who will be utilizing this core set.

DR. ATHREYA: If you omitted that limited agent and recalculated from the same way, would that make a

difference? If they dropped that limited range of motion item out of that six and redid the calculation, would it have come differently?

DR. GIANNINI: I can't tell you because we haven't done that. But again, there were a lot of strong feelings about the limited range of motion because, as Dan said, it showed--methotrexate showed a very large effect size, and also, the physical therapists would add that it is the number one thing they're interested in because it lets the kid do their PT better. So there was a lot of emotion about the limited range of motion. I kind of wondered how it got in there, too, but people like it.

DR. BOWYER: If I could make a comment about that, I really would come down strongly on the side of not including it, because therapy can do wonderful things, even if you are left with range of motion and you're not looking at that and that's going to mess up your calculation of whether the drug worked or not.

DR. WALLACE: I think Dan's point about the core set of data being set up looking at DMARDs is an excellent one because I think, in reality, that's what we want to put our effort in, I think, in terms of treatment of JRA, is looking for those drugs that are going to be along the DMARD lines. I don't know if we want to be spending a lot of time

with NSAIDs and less efficacious agents. I think that's where we want to put our energies and our time, and it makes sense to make the outcome variables that match with those patients who are going to be involved in that.

DR. JOHNSON: Yes, but you would expect a set of outcomes to be given by the nature of the disease, not by the nature of the intervention. I mean, I agree with your sentiment, but--

DR. WALLACE: The nature of the patients who will be in the studies. Right, and there should be outcome variables for those patients that have few joint disease, but those are going to be the minority--

DR. JOHNSON: Okay. If it's true that all the methotrexate JRA patients are polys, is that because a bunch of the Paucis and the systemics have failed methotrexate, or is this because a lot of the severe ones convert to polys?

DR. WALLACE: The second one.

DR. JOHNSON: The second one? The latter?

DR. RIDER: I think, looking forward into the next ten years, there are a number of possible agents. I am hearing this morning, it looks like the group has consensus that the core set will not work for all subsets and I'd like to just try to reach some consensus about what will it do for each of the clinical core subsets.

For example, for poly JRA, I'm hearing this morning that people are not happy with the use of limited range of motion in the core set. Are people reaching consensus about that this morning?

DR. LOVELL: I think the point has been made, and we have the data to look at it objectively and quantitatively--

DR. RIDER: Okay.

DR. LOVELL: --and see, to answer Balu's question, if you drop out that parameter, what happens to the discriminate ability of the core set? So we could answer that question in a scientific fashion rather than kind of a committee-think fashion. So I think it's a legitimate question. We can answer it.

DR. WALLACE: But then if you do drop that out, how are you going to assist hips and shoulders, because you're not going to see swelling. You're not going to palpate swelling. I mean, I think there are some joints for which limited range is all you have.

DR. WHITE: Can I ask a technical question about when you're calculating activity of a joint, and limited range was a part of that, as part of defining activity, so it would work in your comment. So I wondered if--I'm just trying to understand the component of limited mobility that

it plays in defining activity of a joint.

You said swelling was the most common, but when you're looking at hips and shoulders, was the limited mobility the number one thing that defined the activity of a joint? I guess I'm just trying to ask a technical question about how you defined joint activity, because if limited mobility gets counted twice, then, in this core set in particular joints.

DR. LOVELL: I think if you look at the data, the correlation coefficient between number of active joints and number of joints with loss of motion wasn't as high as you would predict based on the fact that loss of motion is part of both criteria. If they had been highly correlated or redundant, in other words, then we would have not put them in the core set. But they weren't as highly correlated as one might predict before you look at the data from the outcome of the studies.

Clearly, the discriminate ability of the active joints and the joints with loss of motion is very different, and the discriminate ability is much stronger with the loss of motion. If you're looking at a drug with the potency of methotrexate, then it does have the ability to do that.

So we were trying to find a tool, an instrument that would clearly distinguish between placebo response and

a true response to the medication, and so when you do that, you have to look at characteristics of joint performance that are fairly or somewhat insensitive to change, and loss of motion is one of those things that's slower and less likely to kind of vacillate than, say, amount of swelling, that sort of thing.

So it really came down to, if you use a drug that's truly effective, like methotrexate, then number of joints with loss of motion really changes over the course of time dramatically with the drug and not very dramatically with the placebo. So that's how it got included.

DR. WHITE: Interesting. Thanks.

DR. JOHNSON: I think, given the presuppositions of the whole procedure that Ed's group went through, it strikes me as hard to justify tinkering with the results, in essence. You either sort of have some faith in the methodology, but the rest of it is all data driven. It is actually more data driven than the adult world drove, in my opinion. There was more sort of judgment interventions along the way in the adult process.

But I think the problem remains, what is its applicability? Is it more efficient with the polys, and if that's really the kinds of patients who are going to go into tough trials anyway, then maybe that's not as important of

an issue. But the other is, is it inclusive enough if you have a lot of sick systemics or sick oligos in there and you want to follow other parameters of disease, but you could incorporate that into your trial without messing around with the core set.

DR. GIANNINI: Yes. Again, I'll emphasize that our mindset was all the way through, we were developing a definition of improvement for anti-arthritis drugs, not anti-iridocyclitis or pericarditis or anything else, with the idea that it was going to be most applicable in DMARD studies, in drugs that we would be looking at in the future. Again, you just said it. If you are doing a study to look at iridocyclitis, then that would be your main outcome, not the core set.

Bonnie?

DR. STRAND: Ed, do you think you could add, for instance, one parameter for each of the subtypes of JRA to choose a core set and require, then, that you have improvement from that point of view and that you would be able to get more specificity?

DR. GIANNINI: But I wouldn't--

DR. STRAND: Rash and fever for systemic, and something else for Pauci, et cetera.

DR. GIANNINI: But I wouldn't add it to the core

set. I guess I'd add it as a separate variable.

DR. STRAND: Right. You add it as a separate thing, but then that could be combined into the outcome. If you, in fact, enroll polys and systemics and a few Paucis who were bad.

DR. GIANNINI: Yes. I think that's what we've been saying, that we're free to--

DR. STRAND: Right. You're basically saying that you have a minimum number of outcomes that must be done and you can add additional ones to it. You're trying to have a situation where you can enroll as many patients as possible in an orphan indication already that's divided into five subclasses of patients, right?

DR. SCHWIETERMAN: Bill--

DR. STRAND: Ten, okay.

DR. SCHWIETERMAN: Bill Schwieterman, Center for Biologics. Actually, Vibeke, you just beat me to the punch, because that was the point I was going to make.

DR. STRAND: Sorry about that.

DR. SCHWIETERMAN: That's all right. It seems to me that the problem with--all these points have been made, but I just would like to echo them. It seems to me the problem with this disease is that there's not enough patients to study if you start splitting into different core

sets. So I think I'd like to compliment the people who went to Italy to do this, to divide this core set, because I think that deriving a core set is going to be useful for industry as a starting point, and then perhaps using that core set in a particular way in a trial design might help you, such as what Vibeke just pointed out.

You could use, for example, co-primary endpoints if you felt strongly about, for example, fever in systemic population, or if you felt strongly that there was another functional parameter that would be helpful for the Paucis, you could include that as a co-primary, or if you didn't feel as strongly, could use it as a secondary endpoint.

In other words, you could use a core set, just as Vibeke mentioned, to stratify patients and to use additional efficacy outcome measures to determine outcome, and this way, you wouldn't necessarily be splitting so much that you couldn't do the trial. I just wanted to make that one particular point.

Also, Ken, I think you also brought this point up earlier about how valuable the core set is in general. I think the problem is, with many of the trials, with the sponsors that we have, getting the sponsors to do the actual pediatric populations is the first step in the hurdle, and by keeping this core set as analogous or as similar to the

adult patient population, to the extent that it's possible, it will simplify at least many of the agency's problems in this regard, because I think the ultimate goal is to get these kids studied.

DR. JOHNSON: And it's a responder index and so we don't have to worry about multiple endpoints, either, which is also attractive.

Do we have other comments from the floor?

DR. MILLER: I wonder just about extending that concept a little further. What about a patient-specific element so that you have--the core set concept is a fine one and I think that should be kept, but rather than a subset-specific, how about a patient-specific element, so you're looking at that additional element would be whatever the parameter, and the global variable analog scale seems to be the most relevant for that particular patient.

DR. JOHNSON: It's in there, though. If the patient's global is in there.

DR. MILLER: No, not the patient's assessment but the physician's assessment of the non-core variable to take into account not only the frequent findings in particular subsets but a particular unusual patient that may not have any of those findings.

DR. TUCKER: There actually--I'm going to talk in

a minute about the functional outcome scales, and there actually is one scale that Ken Duffy has developed that speaks to that and I'll talk a little bit about that in a minute. It actually has a way of patients selecting what's important to them and you can interchange in particular variables that might be important to that particular patient.

DR. HEPBURN: I just wanted to address the comment that had been made about the outcomes being developed, the core set being developed to look at DMARDs. I think we have to leave ourselves open to the likelihood that new drugs will come along that don't fit neatly into the same boxes that we have put drugs in before.

One group of drugs comes into mind immediately and that is the new group addressing TNF, whether they're inhibitors or blockers or whatever they are. These are non-steroidal anti-inflammatory drugs, but they're not the NSAIDs that we know, but they may not be the DMARDs that we know, either, and I think we have to leave ourselves open to the idea that we're going to have new kinds of drugs and we're going to have to address them a little bit differently.

DR. JOHNSON: Bill, do you want to respond to that, please?

DR. SCHWIETERMAN: I think that's an excellent point. I think that the purpose of this conference is two-fold, number one, to establish a basis by which any class of drugs can be studied, but secondly, to recognize that I think we're at the dawn of a new era in many respects with regard to the treatment of rheumatoid arthritis and JRA in general.

I also think that it needs to be kept in mind that we don't need necessarily use an index as a primary outcome measure if there's an agent, let me just say an anti-TNF, that really works well across all areas. Then it's a no-brainer. You can pick a swollen joint count, for example, and have a list of secondary endpoints and everybody would agree that that would work.

The agents for which I think an index are going to prove to be most useful are for the more marginally-affected agents that we usually see. I hope that the anti-TNFs don't belong in that, but they might, because the problem in rheumatoid arthritis, and I think in JRA in general, has been discriminating between placebo effects and between marginally effective agents.

So to the extent that we can power studies with large enough sample sizes and with reasonable enough endpoints if they aren't perfect, I think we're going to be

better off. But for the new ones that come along, if they're working as well as people say they are, then this is all moot here today because anybody--my grandmother could say that these patients are better.

But I don't mean to trivialize this exercise because most of the agents aren't going to be this way and I think that it's important that we develop something by which large, reasonable, randomized trials can be done.

DR. JOHNSON: Two more quick comments.

DR. SILVERMAN: A quick comment. Just playing devil's advocate for a moment, if we would have used gold in polyarticular JRA and lumped everybody together, it would not have worked, yet I think most people in this room feel there is a role for gold in our F-positive polyarticular JRAs. As we are addressing it today, we would have lost that effect. If we do the same in systemics, we might have killed people.

I see this similar to lumping ankylospondolitis, osteoarthritis, and rheumatoid arthritis together, because everybody knows that's arthritis in adults, just like JRA is arthritis in children.

DR. JOHNSON: We will get back to that issue, I'm sure. Next?

DR. PETTY: I have the same concern. I think that

if you don't recognize differences--this is not one disease. Let's recognize that for a start. We're talking about at least three. i think we could argue about more. But we will lose evidence of efficacy of drugs if we are not recognizing the fact that, for example, in the Paucis, at least two of the core criteria will not be applicable.

DR. JOHNSON: Okay. We want to move on now to the next section. The morning section actually is split up into signs and symptoms, quality of life, prevention of structural damage, and remission. Those, in a sense, are candidate claims and they are analogous to some of the things we discussed about in the adult world. What we really want to do is to get feedback from people with regards to whether they think, in principle, this is a laudable goal for a physician treating a patient with juvenile rheumatoid disease.

So next, we are going to go on to the issue of the quality of life and our first speaker is Dr. Lori Tucker from Tufts speaking on improvement in function and quality of life.

II. QUALITY OF LIFE

IMPROVEMENT IN FUNCTION AND QUALITY OF LIFE

DR. TUCKER: I'm not that great at educational media, so is this going to be okay? Can we raise it up a

little bit? Thank you.

I'm going to spend a few minutes talking about how one might measure improvement in function and quality of life in children with arthritis in respect to what's been talked about this morning. I thought it was very interesting that those of us who are looking at children with arthritis and talking about how we are going to measure improvement, people tend to mumble the word "functional improvement". It's sort of thrown around and people sort of say, we're going to measure functional improvement.

What I'd like to do, hopefully, is talk a little bit about the field of how to measure functional improvement and quality of life in children and bring it into a more scientific realm. How are we doing here? Can we get to the next slide?

If you could read this slide--you can look in the handout--basically, I think there are two questions that I've been asked to look at and we'll look at them in sequence. First of all, we want to answer the question, why should we include health-related quality of life as a measure of treatment effectiveness in children with arthritis? Is there a reason to do that? And secondly, if we decide we want to do it, how can we measure health-related quality of life in children with JRA, and it

is not a minor issue.

We are going to spend a little time talking about terminology. It's a very dark room, so these slides don't show up very well. The top two terms, health status and health-related quality of life, I think for people who read the literature become a little bit confusing, but most people who are involved in this field use those terms simultaneously. So health status and health-related quality of life basically mean the same thing and I use them to mean the same thing. People who are involved in this field argue about which one they are using every six months and switch back and forth.

On the bottom, the only thing you can see is functional status, and what I would want to point out right away is that functional status is important. It's a component of health status or health-related quality of life. It's not a separate category altogether.

Then in the middle, there is the term "outcomes", and I think we should try to avoid using the word "outcomes" when we are talking about measuring quality of life or health status in any area because there are many outcomes that one might look at. Health status is one of them, and we have been talking about other ones this morning with the core set. But to say we are going to measure

outcomes is a very vague term, so we'll try and be more specific.

You may or may not be able to see this all that well. People who measure health status like to talk about the definition of health, so what is health? A lot of people use the World Health Organization definition and that's a state of complete physical, mental, and social well-being. Well, that's wonderful, but even on a good day, most of us can't claim that. So I think to say we're going to give drugs to children with JRA and that's what we're going to get is maybe not so realistic.

I happen to like the definition that Ed Schor proposed a couple of years ago and that is what we're really trying to do when we treat patients is we're trying to enhance someone's ability to function physically, emotionally, or socially. So I'd like to keep that in mind, because if we look at the core set and all the things we've talked about this morning, we really have been looking at perhaps physical functioning, enhancing or how we can measure physical functioning, but we haven't mentioned anything about social functioning, emotional functioning.

Everyone who does this kind of work likes to have a conceptual model, so here's my conceptual model. I took this from an article written by Guyatt, et al, and the

reason why I like this model is it's clinically oriented, and that is if you look over to the left-hand side of the slide, what we start out with is patients have biologic and physical variables. They have a disease or an illness, and that causes the next thing, which is they have symptoms, and those are things that we can measure. Those symptoms or that illness leads to changes in the patient's functional status. So far this morning, we've gotten that far.

All of the arrows are pointing to the right, and some of these arrows probably could be double arrows, but if you look over at functional status and go further to the right, well, the patient's functional status and their symptoms actually lead to them having feelings about what their general health is.

I'd like to point out that there have been some very nice studies that show that, at least in adults, if you ask a single question about patients' general health perception, that that may be the best indicator of the patient's outcome in certain circumstances. So there's a good reason to ask that. Then all of those things impact on what the patient's overall quality of life is. So that, generally, is the model to think about.

There are a couple of points that are listed in the handout. First of all, I think the outcome that we're

all most interested in, patients and clinicians, is patient benefit. It's not how many joints are moving or not moving or how long you're stiff in the morning. It's the patient's overall benefit, and some of the physiologic measures of outcome, like sedimentation rate, are important to us as clinicians but really may be of very limited value to children and parents because they're more interested in functional capacity, general well-being, and their child's ability to be involved in normal childhood activities.

So in answering the questions, why should we measure health status in showing whether a drug is effective in JRA, it's because that's what's important to children and families.

Certain children who have the same measure of clinical outcome have very different functional status or quality of life, and I'm sure everybody has seen patients in their clinic, one child who has very severe systemic JRA with very destructive arthritis who is president of her class and in plays and very functional, and you see another child who has two joints involved who is completely functionally disabled. That gets to this idea of measuring the area under the curve for functional disability, but somehow, we need to get a handle on that, and functional outcome measures may help us do that.

We need to talk about a few concepts of measuring health status to understand the measures that we have available to us and to be able to make choices of what measures might be worthwhile in drug treatment trials of JRA.

First of all, there's the concept of generic health status measures versus condition-specific measures. Generic health status measures are those that measure concepts that are relevant to everybody in a population and it's not specific for age, sex, disease, or treatment. In that case, you're able to administer these in a generic measure to patients with a variety of diseases as well as healthy populations, and what it allows you to do, it allows you to compare across population, compare the impact of different health care programs or systems, and understand the burden of illness.

However, these kinds of measures may be not too sensitive to small changes in a specific condition because they weren't designed to look at the small indicators of improvement in a disease like JRA. So they may be insensitive to that kind of change and they may be less applicable in the area of using them for drug treatment trials.

Condition-specific measures, on the other hand,

are measures that are specifically designed for a specific condition and those measures are designed to take into account the particular problems that one might find in a particular disease, and, therefore, they should have greater sensitivity to change for that specific condition and you have better comparison within the disease group. However, you cannot administer them to other population groups and you can't compare across populations.

The other thing that--I think people have been throwing around a lot of terms--is the idea of measuring functional status versus measuring health-related quality of life, so maybe we can just define that a little bit before we start talking about measures.

I think functional status, very simply, is measuring the patient's ability to perform specific activities. So anybody who has looked at, let's say, the child HAQ can see that there's a list of specific activities. Can you open the door, put a sweater on, various things like that. What's your functional status?

A health-related quality of life measure goes further and what is tried to do in that area is trying to define how the patient's health or illness impacts that patient's ability to perform usual activities. So for children, usual activities, such as going to school, being

involved in sports, going to the mall, having overnights with friends, and it includes things like self-esteem, as I mentioned before, perception of one's health, and mental health.

I think in children, one of the things that's important to include in the health-related quality of life measure is a measure of behavior, because in many ways, it's an indirect measure of mental health in younger children, and also family impact, because the family is involved in this illness, and functional status measures don't look at those types of things.

A few years ago, 1987, Bob Meenan wrote a review article in Pediatric Clinics of North America basically setting out what pediatric rheumatologists might have to do to develop health status measures for childhood arthritis analogous to the AIMS that he developed in adults, and it's a nice sort of outline of the field.

He defined some of the major components of health status that one might want to measure and I have them listed in a table here because we're going to talk about--you'll see some of these come up when we discuss particular JRA-related measures that are available. These are basic domains of health and include things like physical health, functional status, symptoms, mental health, behavior,

self-concept, social health, social activity, and what's called role performance, a term I don't like so much, but things like can you go to school, can you go to work, how do you do in normal activities. So if you can keep these components in mind, then you will be able to compare what kinds of things do the measures we have available to us, what kinds of things do they measure.

We have some specific problems that are inherent in measuring functional status in children and quality of life that people don't have in adult rheumatology, let's say. First of all, I think a very important question that still is hotly contested is who we're going to ask for the information. Are we going to ask the child, are we going to ask the parent, or are we going to ask the clinician?

I think most people would like to get patient-based assessments, but this becomes very difficult when the patient is three years old. How are you going to get a patient-basis estimate and what kind of problems are there inherent in accepting the parent as a proxy for a child assessment, or in an adolescent situation, if you ask the adolescent alone, is that adequate, or do you need more information from parents? That's a very long discussion, but it's a problem that needs to be dealt with and decided on.

Secondly, we have to deal with developmental changes. The difficulty of looking at an instrument that says it's going to be effective for children, measuring health status in children who are age one to age 18, poses some real difficulties, because obviously, a one-, two-, or three-year-old child is doing very different things than a 15- or 16-year-old child. How is that one measure can address all those issues and how can we score that measure and how can we compare those patients? These are problems that we need to think about.

The other thing is, how do we deal with the range of normal abilities in each age range? In the adult population, there is sort of a norm of normal abilities. In childhood, at each age range, there is a range of abilities, and so that makes norming these kinds of questionnaires a little bit difficult.

Before we start looking at health status interests and thinking about comparing them, I thought I would put down some of the qualities of what might be an ideal health status instrument so we have something to aim for, and these are mostly somewhat personal opinion but also taken from the literature.

First of all, I think most people would agree that what we would like to have is some sort of patient-based

assessment, even if it means that in certain populations in pediatrics we have to rely on parents. We want to make sure that it measures all important domains, so going back to Dr. Meenan's list of domains.

It needs to be something that's practical. It has to be easy to give out, administered in a clinic, and it has to be easy to score, because otherwise people are not going to use them and they're not going to end up being useful.

We obviously want to pick an instrument that's sensitive to change over time, so responsive, and that's very critical when you're using an instrument in a drug treatment trial. We'd like an instrument that has some defined relationship with clinical indicators, and this gets to things such as phase and content validity. In other words, it would be useful to know that a certain change in score correlates in a way that makes sense to us clinically with some of our clinical indicators.

Lastly, I think an issue that we really don't have good data to support yet is we need an instrument that has interpretable scores, because if you select a health status instrument as part of your drug treatment trial and you get numbers, what you need to know is does that change in number represent a trivial improvement or deterioration or an important improvement or deterioration? I think we probably

don't have enough information in most of the instruments we have now to answer that kind of question, but I think that's very, very important.

We're going to talk a little bit about various health status measures. This first slide lists, not exhaustively, but some of the generic health status measures that have been developed in pediatrics. I wish I had a pointer. I'm going to go through them very quickly because they may or may not be the most appropriate kinds of instruments for pediatric--thanks so much. That's great.

I'm going to start at the bottom, actually. These instruments at the bottom, the WeeFIM, the Tufts Assessment of Motor Performance, and the PEDI, these are instruments that actually were mostly developed for children with severe disabilities, cerebral palsy, and other types of disabilities. Interestingly, several of them are physician reporter instruments. They take a lot of time to administer and the physician has to get the information and they look at different age ranges. They don't cover quite the whole age range. We've used occasionally this measure for children with dramatamyocitis [ph.] at our center and it really is purely a more functional generic assessment tool.

The Rand Health Insurance Survey developed a generic health status measure for a very broad age range of

children, which is very general, and used it in a large study. It's a parent report measure.

Barbara Starfield developed the CHIP, which I think is a nice name, for adolescents, which is an extremely exhaustive profiling, very long profile that looks at some very interesting concepts in adolescents, such as risk-taking behavior and a variety of other things which--but it's never been studied to look at change over time and it's not really been developed in that manner. It's very limited for the age ranges we might be looking at.

Ruth Stein's group developed the functional status measure here, which goes over an entire age range. It's a parent and a child assessment form and it has been used in large populations of both health and some chronically ill children but never looked at in children with JRA specifically and there's no information about change over time in a treatment trial situation.

The Child Health Questionnaire is a new generic health questionnaire that has been developed by people at New England Medical Center who were involved in developing the SF-36, John Ware's group, and this questionnaire is just being made available now. It's a generic health status questionnaire for ages five to 18. There's a parent form and then an adolescent form for 13 to 18-year-olds. That

form has been normed on healthy populations and some chronic disease populations, including our clinic population, and I'll talk more about this one in a bit because we actually--this shows up in one of the JRA-specific questionnaires.

I'm going to spend very little time--I don't have a slide discussing health status measures that are used in adult rheumatology, and I suppose as a pediatric rheumatologist that's a particular bias, so I wasn't going to spend a whole lot of time discussing them.

There are certainly a number of very well developed and very well validated adult rheumatology health status measures, and most of you have probably heard of them, such as the AIMS and the modified HAQ and the MACTAR from Canada. These measures have not been looked at very well in a pediatric population except for the AIMS.

But basically, I would propose that they're not appropriate for use in pediatrics and the domains that they look at are not appropriate for childhood activities. For example, there are questions about adult work activities and various hygiene and social interactions that are completely inappropriate for any child. These measures don't at all address family impact of disease in childhood, so that certainly they could be looked at, but we have available

measures now for children and we probably should be looking at those.

I wanted to spend a minute talking about the SF-36, which is what's on this slide here, because people have asked me about it and I think it might help just to explain what it is. The SF-36 is a generic health status survey that was developed by a group who used to be at Rand Health Insurance and now are at the Health Institute in Boston to look at adult patients, healthy and disease controls. It's basically--it's been very, very successful in the field of adult health status measurement.

This questionnaire is actually reported to be validated for adolescents as young as 15. However, I think the actual amount of data that was collected to validate this instrument in patients who are 15 to 20 was quite small, if you ask to try and pin them down.

The measure is quite good in that it measures all of these domains over here, so limitations in physical activities due to health and usual role activities due to physical health or emotional problems, limitation of social activities due to physical or emotional problems. There's a pain question, general mental health, vitality, how much energy you have, and a general health perception question. As I said, it's really been used and quite extensively in a

variety of circumstances in adults.

We did a short pilot study in childhood lupus patients to look at using the SF-36, and just anecdotally, I think it showed some significant limitations in the area of measuring social and role activities. There were single questions about social and role activities but really did not discriminate very well among the adolescents, and they had some difficulty in actually understanding those questions. So it may or may not be the best measure for adolescent patients in general.

The next thing we're going to do, you have a table in your handout which compares at least all of the actively being worked on and available health status measure for use in children with JRA, and I'm going to go through each one of them and give you some background on each one and try and compare them on a variety of features, and then we'll talk about psychometric properties at the end.

The first one I'm going to talk about is the Juvenile Arthritis Functional Assessment Report, which is the JAFAR. This was developed by Dan Lovell and his group in Cincinnati. It's a functional status assessment tool that was designed for children with JRA, so it's condition specific. It's for children ages seven to 18, and there are both child and parent self-report versions that have been

tested and validated. There are 32 items, so it's a relatively short questionnaire, and it is very easy to administer and use, or looks to be, in a clinic setting.

It asks patients for how have you been able to function over the week preceding making out this questionnaire. The questions address--there's an ability scale, so it has a list of various functional activities that the patient is asked to rate whether they're able or not able to do, whether you use aids or devices, whether you need help from others, and there's a pain visual analog scale included in the JAFAR.

The next one we're going to talk about is the child HAQ. This was a modification of the adult HAQ from Gerkepal Singh [ph.] and this is a functional status assessment which is supposedly applicable through a very broad age range. There are 34 items, but if you look at the items very carefully, very few of these items are actually applicable to younger-aged children and I'm not sure how you could actually use it in a very young age population because there are so few of these items that you would be scoring the questionnaire on, only three or four items. There may be a way to get around that, but I find that to be a bit of a difficulty.

It's quite easy to administer and use, and one

thing that may be useful is that it links with the adult HAQ, so that if you were doing a very long-term outcome study, you could potentially move patients from using a child HAQ into the adult HAQ and you would be measuring similar domains of function.

The next one we're going to talk about quickly is the Juvenile Arthritis Quality of Life questionnaire. This is a questionnaire developed by Caren Duffy [ph.] and his group in Montreal. This is a functional status tool, but it also is a quality of life tool. So it's different from the previous two we talked about and it's got a very broad age range, children one-and-a-half to 18 years of age.

It's a parent report questionnaire. It's quite long, 74 items, that fall into these categories, so it includes psycho-social symptoms as well as fine, gross motor, general symptoms, and pain. There's a bit of a complicated item process, and it does get to the question that was asked about selecting items for a particular patient.

The patients are asked to select out of a list of seven or eight items the three that are most important to them and to rate how they are functioning on those items, and if they don't find any items in that list that apply to them, they can write in their own and since a change is

measured on those items that the patient has selected when they do the questionnaire a second time, so that there is some built-in ability to measure sensitivity to change in that particular patient.

However, what it means, if you look at a population of patients, you're not scoring all the patients on the same items. The patients are selecting their own items. I found it a little complicated for myself, so I wondered how this might work out, depending on what parent educational levels are.

The JASI, Juvenile Arthritis Functional Status Index from Virginia Wright in Toronto is a functional status JRA-related score, which is a scale which is for children eight to 18. It's a child report measure, which is great, but it requires an interviewer, so I think in a clinic situation it might take quite a bit of time because it's very long, 94 items. But they also have things in there about school and extracurricular activities which some of the other measures don't address.

Lastly, the Juvenile Arthritis Health Profile is a profile we've been working on in Boston with people at the Health Institute and at the American Academy of Pediatrics. This profile is, again, a functional status profile and quality of life scale applicable to children five to 18

years of age. There is a parent report form that has gone through preliminary testing and now there's an adolescent form for children 13 to 18. It is long, 94 items, and this questionnaire has both generic scales and JRA-specific scales.

So we took this child health questionnaire that addresses all of these areas, includes mental health, general health perception, behavior, self-esteem, and family impact. We took that in toto and then we developed JRA-specific scales for areas that we thought would be more specific and sensitive to change over time in children with JRA. So we added in more questions about gross and fine motor function, role activities, morning stiffness, and school function.

This questionnaire potentially could link with the SF-36 because the generic part of the questionnaire is developed by the same investigator. So you could potentially use it over a long period of time with the SF-36 in older patients.

I'm being told I don't have much time, so we're going to go through this very quickly. Just to give you an idea of what happens when you give out a questionnaire like this in a clinic population, what kind of information do you get? This is basically, this generic questionnaire, child

health questionnaire that's part of our child CAHP form, given out to 78 children with JRA, and these are the scores you get on the various domains of functioning, and what you can see is certain things that you would expect, is that basically their physical functioning is not quite up at a normal range, but some of the things, such as emotional behavior, are fairly normal, whereas the general health perception--and these were parents who answered this form--was fairly low. Parents didn't think their children were as healthy as other children, and that's what one might expect.

The other thing that you can do is you can see that if you try and separate out patients by a global physician JRA severity or activity score, that some of the questions on these scales separate out the patients quite nicely. So if you just look at the red side of the slide here, this is basically asking the parents a general health perception question, how healthy do you think your child is compared to other children? As you can see, children with mild disease severity score fairly well on this, whereas children with severe disease don't score well at all. The hope is that as we study this, that we'll see that we can see changes over time as the patients either improve or deteriorate in a drug setting.

I think we'll skip this. We don't have time.

Lastly, I just wanted to mention a little bit about these instruments and how they've been tested. The instrument that we've just been talking about, the CAHP, we've done some preliminary validity and reliability testing on 80 subjects and it has shown to be excellent. The responsiveness we are going to work on now in a larger trial involving five centers and 250 patients.

The JAFAR--and I took these from the literature, so if people have other information, they should raise their hands later--has excellent validity and reliability testing, but I haven't yet seen a report of the responsiveness of this index over time, similarly for the child HAQ.

The JAQQ actually has excellent validity and reliability testing and there is some early data that shows there is very good responsiveness to change over time because that's how this index was designed.

The JASI also has excellent validity and reliability but had just not been reported in respect to responsiveness.

There are some questions that we need to think about. First of all, I think we need to have more information to be able to interpret scores from these questionnaires. Without this information, we can't really

make any assessment about effectiveness of a treatment. I think we need to look at--there's a very broad range of ability and disability in children with JRA and that may be a problem in using some of these measures, and we've already talked about that this morning, that Pauciarticular JRA patients in Dr. Lindsley's study had very little disability on a child HAQ. That's because they basically have a ceiling effect. They're all doing well, so you can't measure change. So we need to think about looking at these instruments in different populations and figuring that out.

There are still some technical issues that need to be addressed. There are no translations, or very few translations of these instruments for non-English-speaking population. Nobody has done any work to validate them in non-Caucasian groups. That may be a problem, particularly if we start using them in an international basis.

I think the major question is, we have to decide, do we want to measure functional improvement alone, do we want to measure quality of life, or do we want to measure both if we can? That's it.

DR. JOHNSON: Thank you very much.

We're going to move on to the next speaker at this point, who is Dr. Sanford Leikin from NIH who is going to make some comments in this domain from the point of view of

an ethicist.

QUALITY OF LIFE: ETHICAL ISSUES RELATED TO PEDIATRIC CLINICAL THERAPEUTIC TRIALS

DR. LEIKIN: Modern-day research ethics is based on the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. That commission was created by Congress in 1974 to draw up rules to protect patients who participated in clinical trials.

In its deliberations, the National Commission considered the boundaries between research and practice. It defined practice as those interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success.

Research was specified as an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge. Research and practice can be carried on together so long as the element of research undergoes review for the protection of human subjects.

The National Commission identified three principles that guide human subject research. They are respect for persons, beneficence, and justice, and I will amplify on them a little later on.

The National Commission also directed its attention to research involving children. Although some individuals had raised doubts about doing research on children that did not offer direct benefit to them, everyone agreed that research that did offer a benefit was ethically justified.

Based on the principle of beneficence, which requires securing persons' well-being and protecting them from harm, the commission strongly recommended that research should be conducted on children because in numerous instances there is an absence of a suitable alternative population of research subjects.

Clinicians who use new interventions usually must rely on data obtained in research on adults. This practice may be hazardous since children differ in important ways from adults. In these instances, the commission was also concerned about the negative consequences of not conducting research on children. The consequences might include perpetuation of harmful practices, introduction of untested practices, and the failure to develop new treatments.

Another reason to involve children is the satisfaction that they might gain in knowing that they are helping others or that it could encourage their moral development by stimulating altruism.

While the commission concluded that research involving children is important for their health and well-being, it recognized their vulnerability arising from their dependence and their immaturity. This vulnerability raises questions about involving them in research.

But the commission asserted that such ethical problems can be offset by establishing conditions that must be satisfied prior to their involvement. Most important of these conditions concern obtaining parental permission and the assent of the child. Recognizing that children cannot give legal consent, the commission recommended that prior to the child's participation in research, the parent's or guardian's permission should be obtained.

Soliciting parental permission, as distinguished from consent, satisfies the principle of respect for persons by respecting the child's needs for care and protection and by respecting the authority of parents to make decisions regarding their children's lives.

Obtaining assent also accords with the ethical principle of respect for persons. That principle not only requires respecting the decision of autonomous persons but also compels honoring the choices of individuals with diminished autonomy to the extent that they have developed the capacity to make choices.

The Federal regulations define assent as the child's affirmative agreement to participate in research. The regulations also state that mere failure to object should not, absent an affirmative agreement, be construed as assent.

The benefits of seeking assent are it provides useful information to minors, it enhances the child's sense of self as an active and responsible determiner of what happens to his or her life, it promotes a trusting relationship with the researcher, it encourages a greater feeling of confidence and effectiveness, and it increases the minor's sense of self-esteem.

It is the responsibility of IRBs to assure that assent is sought when it determines that the children are capable of providing assent. The IRBs must recognize that the children's decision making capability varies with their cognitive and emotional development and life experience. Another factor that must be taken into account is the complexity of the issues involved.

Using the standard of a low level of factual understanding and the ability to express a preference, there is general agreement that children greater than seven years of age can give a competent assent. A higher standard, equivalent to adult capacity for consent, can be given by

most adolescents greater than 14 years of age.

The information provided during the process must be comprehensible for that developmental level. The important items to be related are the child's role in the research, that they can ask questions and get answers, and that they can refuse to assent or can withdraw from the research.

A major caveat in seeking assent is the acquiescence of children towards adults, particularly those in authority, like parents and physicians. Children's conformity is most striking in pre-adolescence and early adolescence. Younger and middle adolescents may also be more trusting of investigators than older adolescents. Younger children are less likely to be perceptive of the reality that the clinician-researcher has a vested interest other than the patient's welfare.

Conformity can also be modified by the manner by which it is sought and by the presence of parents who have agreed to the proposed research. The child may perceive that parental approval has made participation mandatory. While it is appropriate to seek parental consent or permission before seeking a child's assent, whenever possible, requests for participation of children should be introduced by the sentence, "Your parents have indicated

that it is okay with them if you take part if it is also okay with you."

While the dissent of the minor should always be taken seriously, the Federal regulations also do state that if the IRB determines that the capability of some or all of the children is so limited that they cannot be reasonably consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or welfare of the children and is available only in the context of the research, the assent of the child is not a necessary condition for proceeding with the research.

I think this has a particular significance for the conduct of therapeutic research in a life-threatening or a chronic debilitating disease, such as JRA. While it may be appropriate from a regulatory standpoint to ask that the requirement for assent be waived, I would discourage that such a request be made, particularly in the case of adolescents. Excluding them from decision making not only is disrespectful, because there is a growing consensus that as the child matures, his or her views are due to a growing degree of deference. Also, if they're excluded from the decision making process, it is less likely that they will comply with any regimen that is offered.

Not very much is known about the process of enrollment of children in protocols and the adequacy of the understanding attained. What is known indicates that older children do not have a better understanding than younger children. The children in general have a better grasp of some of the concrete aspects of the protocols, such as the potential benefits to themselves of participation, the duration of the study, and their rights to ask questions and to withdraw.

They are less likely to appreciate the abstract features, for example, the purpose of the study and the availability of alternative risks. Significantly, they also did not know the procedures or risks involved in the study.

While these few studies paint a rather dismal picture of the assent process, it must also be recognized that studies undertaken in adult subjects of their understanding and decision making regarding participation in research are also quite disquieting, and on that negative point, I will quit.

CRITICAL RESPONSE/GENERAL DISCUSSION

DR. JOHNSON: Thank you very much.

Let me just try to frame the discussion. We will go for another 15 or 20 minutes and then we'll be about 15 minutes behind, but I think that's tolerable.

We decided at this point to have the whole issue of ethics addressed head on. Obviously, everybody in the room probably has and should have important feelings about the heightened sort of ethical perception that pertains to children and kids.

In parallelism with what we did in the adult world, the notion--one of the purposes here is really to kind of help stimulate research for new products in JRA and the perception would be that a company would come in after the standard claim, which is the signs and symptoms claim, and achieve that after trials of x-months or whatever. But in addition, they could then fold that development into pursuing one of these other claims that we're discussing. We've touched on the health-related quality of life one now and we're going to touch on x-ray changes and remission after the break.

Presumably, these would be longer trials, and so I think the whole ethical issue becomes more paramount when you're talking about a controlled setting going out a year or more, and that's why we brought up the topic at this point in time.

Why don't we go first to our four commentators and see if they have comments in this regard, and then we'll open it up to the floor.

DR. CASSIDY: I'd like to make a series of comments on these two discussions. The basic point is how well is either the child or the parent understanding the questions that we are asking them.

We first looked at the JAFAR in 30 children with JRA and even I was amazed that the correlation of this instrument for severity of disease, both on clinical and laboratory scales, was very high, and these were blinded studies and we're continuing that study, but we were concerned about the applicability of this instrument to the younger ages, so we decided to begin to look at the JAQQ.

And as we had done with the JAFAR, the first thing we did was to go back to the School of Education and a particular group there that evaluates instruments for understandability, both connotation and denotation, and as you remember Shaw's comment about the English language having been developed in England and seldom spoken in North America, in Missouri, we deal with a variant of that that we call Ozark English.

Our preliminary look at the instruments and the preamble that we would have to submit with them indicated that we were going to have great difficulty translating these down below the tenth grade. Most of our public, and we're dealing here with the parents, actually speak at the

eighth grade level, which has something to do with the upcoming election, too.

[Laughter.]

DR. CASSIDY: But as time goes on, the eighth grade level actually deteriorates to the sixth grade level. So the first thing that I think that we must reexamine with all of these instruments is how well is our parent or our child, if older, actually understanding them?

For instance, one of the first words in the JAQQ is "awakening". How does your child feel upon awakening, and awakening is not in eighth grade English. We all have trouble with that because of our past education, but these are well developed, computer driven instruments of evaluation.

That then comes to the ethical issue, and I have been on the IRB. Actually, very little attempt is made, even with the lawyer and the representatives of society on there, to look at the consent forms that we administer to patients, and I would allege that few of our patients are understanding those instruments and I think that that is a major defect in our ethical approach to these issues.

Then the last issue involves an NIH study that we had sponsored for some five years looking at the psycho-social functioning of both children and parents with

JRA, juvenile diabetes, and then a control group of "normal" children. There were about 100 in each group, and in the JRA group, we found an interesting biphasic trend in the functioning of the mothers, and I will confine my comments only to the mothers because those are the ones that usually bring our children in and those are the ones who would be answering our health evaluation instruments.

There was a marked improvement in the psycho-social functioning, which would be reflected, I believe, in their answers on these instruments during the first six to 12 months, and then that psycho-social functioning, in spite of continued support from the clinic, deteriorated pretty much to entry levels.

So I think that there are two points here that are of concern to us. One is the basic understanding of the instrument, and secondly, the cognitive approach to that instrument depending on the mother's own psycho-social functioning state.

DR. JOHNSON: Other comments?

DR. WHITE: I have only one other comment in my experience in trying to assess developmental stages in adolescents, in trying to translate it into adult functioning, and the biggest issue is actually ethnicity. In other words, language is one thing, but the expectation

of developmental milestones in different ethnic groups and even within ethnicities and neighborhoods is so broad that over a short term, we have found that right now, two years is too short in looking at issues of job readiness. That is a powerful comment, though I am not sure you are looking at that as an outcome in a drug study.

But whatever it is that you choose, these kinds of outcomes really depend on long-term changes and the normative, the broad component of what's normal may make it impossible to look at. I don't know. It's going to be very hard. It's going to be very hard to look at, depending on what you--certainly, other things you can look at, but I just want to throw that out as something that's been a very powerful issue as we've looked at it. The norming of these things had to be done in very particular arenas.

DR. JOHNSON: We're really interested in trying to get some feeling as to whether or not the JRA community feels in principle that some sort of functional quality of life achievement is desirable. I mean, it's one thing to do that and the other thing is--if there's a broad agreement about that, and then, obviously, that should be a stimulus to pursue these instruments and validate them and all that.

This, again, grew out of an analogy with the adult world, where we're getting submissions and there's been this

perception that the disease will ease up, that the x-rays will march along in the adult world, and I know it's not equivalent in the JRA world, but I'm just giving you this as an example.

Now, developers are going after x-ray arresting agents and they want to know how to asses them, and we think that, in conjunction with clinical success, x-ray arrest is credible, you know, a priori, it's credible, and that's what we need to get some feedback regarding these other three claims that we're going to be talking about, quality of life and remission and x-ray retardation.

DR. ATHREYA: I really need data in adults with the quality of life measures in adults with arthritis, lupus, et cetera. How good is it? Do we know?

DR. JOHNSON: Somebody can better answer that than I, but I think it's much more advanced in the adult world.

DR. TUCKER: Yes. There's a lot of data looking at using a variety of health status measures in adult rheumatology.

To answer the question, is this a worthwhile endeavor, I think people have just adopted the feeling that it is worthwhile and important to measure.

There are some other interesting, I think, applicable studies. There is a nice study done by

orthopedists looking at elderly individuals who have knee replacements, and what they looked at is comparing the physician assessment of patients' outcome versus the patients' assessment of their outcome, and what they found was there was very little correlation.

The physicians were raving about how tight the ligaments were and how improved their range of motion was and how much further this little old lady could walk up the stairs, but this little old lady--actually, many of the patients were marginally improved in respect to their social functioning or their ability to improve their activities.

When you start looking at drugs or interventions, which cost money, is it important that the doctor thinks that the patient can walk further or is it important that the patient or the child and the family report that, in fact, they have better functioning? I think there's evidence to support that.

DR. ATHREYA: That is actually the reason I was also asking. Like you said, with Pauciarticular type, you find very often the parents are not satisfied, even though I know how many of those kids with the systemic onset type. There are lots of satisfactions as improved or there are people, the personality. Here, we are talking about younger kids where we have a proxy, which is the parent, and their

perception, that's so different.

There are kids with high fever, a lot of problems, the patients are always managing pretty well, and then there's another one with just one joint. Every time the mother shows up, her face looks like the whole family is falling apart. So the perceptions affect some of these things.

A functional measure, yes. Quality of life, is it realistic?

DR. TUCKER: There are some ways you could potentially control for that, and we've talked about actually adding a question, looking at what you were talking about, which is parental depression index or whatever and using that to control for some of the other scores. We decided not to do that, but there is this parental impact score.

We just don't--I mean, we don't have enough data to be able to answer your question, but my hope is when we get 250 patients over 18 months, that we can start looking at some of that and pulling it out. Certainly, we would look at--nobody has looked at these quality of life indices in a large enough patient population to pull out patients who have Pauciarticular disease and look at them over some time versus those with polyarticular disease, and these are

very simple questions but we need a lot more data.

It may be hard for everybody here to make a decision on whether this is a worthwhile thing or not, or certainly what instrument to use, because the data is just not there to really answer many of the questions yet.

DR. JOHNSON: You're thinking it's worthwhile in principle? Is that what you were saying?

DR. TUCKER: I think it's essential in principle, really. I think if we don't include those kind of measures, then we're only looking at some very limited outcomes.

DR. RIDER: The quality of life measures that you mentioned, would you think that a general tool would be useful and specific and sensitive enough, or a more disease-specific measure?

DR. TUCKER: I'm kind of a biased observer, I suppose, because I think that actually, if you can, it's nice to have both, and that's why the scale that we developed has both. It has a generic measure, which is basically plopped right in there, and some condition-specific skills that are added on.

If you wanted to look at pediatric rheumatology as a whole, you could say, well, this might be an effective mechanism for pediatric rheumatology as a whole because one could develop dramatamyocitis scales and use essentially the

same index, the generic index, and just add dramatamyocitis scales or lupus scales and have the same general generic scoring on the whole population of children with rheumatic diseases, and that might be useful to us as a field.

DR. JOHNSON: But we have no idea how sensitive the generic scales are to interventions?

DR. TUCKER: No. There is no data on that.

DR. LOVELL: I think the functional scale is a little bit farther along in terms of some of these issues. We took the JAFAR and put it into the polyarticular JRA gamma globulin trial and the effect size in that trial was comparable to the effect size with joint measures, an effect size of about 0.7, I think it was, wasn't it, Edward, about that?

DR. GIANNINI: Actually, I have a reprint somewhere. I was looking for it as you talked.

DR. LOVELL: Yes. It is 0.7 or 0.7, so it had a moderately good effect size, so it represents an acceptable sensitivity to change in that particular trial. It compared to other more traditional outcome measures we used in that trial. Now, that was in a polyarticular JRA group. So I think the question still stands as to what would happen in a Pauci JRA group and I think it probably wouldn't be as good.

Both the JAFAR and the childhood HAQ have been

used in a variety of settings. They've both been used in Portugal and both translated into Portuguese. The JAFAR has been used in Mexico, Russia, and one of the Scandinavian countries, and in all instances, the measurement characteristics were almost identical to the measurement characteristics demonstrated in the original trial.

DR. GIANNINI: Dan, the treatment effect size was 0.6 in the IVIG trial.

DR. JOHNSON: One quick comment. Even if one was insensitive and the other was sensitive, you could ask of a drug that it improve your disease-specific measure but it didn't permit deterioration of your general health status measure if you didn't think it would improve it.

From the floor? Could you identify yourself, please?

DR. SUNDELL: Robert Sundell from Boston Children's Hospital. I've had several concerns about the usefulness of functional measures in pediatrics. Basically, my biggest concern is that since they still are in a relatively early stage of development, they will require lead time in validating and demonstrating their applicability and this has to be added on to any delay that will be inherent in a clinical trial of drugs and children and I think that's something that we are all here today

trying to avoid.

Secondly, with the increasing migration of populations, if we want true measures of how children are doing, we're going to probably be looking at children in different centers with different examiners, introducing an additional level of variability into these measures, and over the short term, since children's abilities change over time because of their development, they are so different than the adults, I think, again, that the validity and usefulness of these functional measures in children is a problem.

DR. JOHNSON: It will take time. You could perceive a company going after a simpler claim with the quality of life claim occurring post-approval, once those trials were finished, for instance.

DR. SUNDELL: But then you would have had to prove that these measures are useful over time in different centers with different examiners, since HMOs are going to change, doctors are going to change, clinical centers are going to change, patients are going to move. There are so many variables that we have to measure and validate before we could say that those claims are useful.

DR. JOHNSON: Yes. That is undoubtedly true.

DR. RIDER: For quality of life claims, would 12

months be a time that people would feel is reasonable? Would they go after a shorter trial time or a longer trial time?

DR. JOHNSON: You've got to have a control that long. That's the real issue here. It doesn't have to be placebo, necessarily, but--

DR. WHITE: What was your parameters for short and long?

DR. RIDER: Twelve months is what's been proposed for adult rheumatoid arthritis. Are people proposing that--

DR. WHITE: That's the short or the long?

DR. RIDER: That's what's been proposed for adult rheumatoid arthritis. Would people propose keeping JRA as a 12-month clinical trial for quality of life claim or would they shorten that or lengthen it?

DR. GIANNINI: From a practical standpoint, correct me if I'm wrong, but nobody's done a study with a quality of life tool in a longitudinal fashion, correct?

DR. LOVELL: Correct.

DR. TUCKER: This is why I wouldn't touch this question, because we don't have the information.

DR. GIANNINI: Right.

DR. TUCKER: I mean, I think we could sort of intuit that--

DR. GIANNINI: Speculate.

DR. TUCKER: --probably less than 12 months is going to be inadequate, but whether 12 months is long enough or not--

DR. JOHNSON: But this issue is not whether the instrument might succeed or fail here. The issue is, is one year quality of life for a JRA kid important, and if that's true, then if you do your studies and your instrument fails, that means the instruments are inadequate, not that the time judgment was incorrect. So we're really asking for an opinion about the notion of quality of life and the notion of JRA. We don't have to make a de decision on these things, obviously, but eventually, we will have to think about this.

DR. LOVELL: I could make a comment. I think one of the strengths of this revision of the guidance material is that it expands the potential for trials in JRA beyond signs and symptoms, and so it is quite provocative in that way and I think we all agree that quality of life, as opposed to SED rates or number of active joints, is really what we as physicians are trying to get for our patients.

So I think that's very well taken and I applaud the fact that it's in the guidance materials. Your point is well taken, also, that we need to distinguish between the

kind of shortcomings of our current level of measurement tools and knowledge of those tools to the overall validity of the concept, and I see no reason why in children quality of life assessment periods should be dramatically different than that that we've derived in adults with much better data, I think, and more experience.

DR. JOHNSON: I mean, there's a lot of dimensions to that question, really. Another facet of it is, what actually is your measure you're going to use? Is it simply the final measure versus the beginning measure, ignoring everything in between? That really seems a little counter-intuitive, and we've sort of swung back to some kind of multiple measure.

So you could envision that a test in a trial for quality of life would be that your JAFAR or whatever, your measure succeeds in eight out of the 12 months or something like that, or it succeeds in four out of the last six months or something like that. So there's a lot of different aspects to this.

Yes?

DR. PETTY: Do I assume that we are talking exclusively about quality of life measurements, not functional outcome measurements?

DR. JOHNSON: Well, I think they sometimes get

blurred together, is what I've heard here, and--

DR. PETTY: But it seems to me that we have a better understanding of functional outcome measurements, which we could probably all agree with, more or less, and we have very little understanding of quality of life measurements.

DR. JOHNSON: Yes. I--

DR. PETTY: It seems to me we stand to lose the usefulness of the functional outcome measurements by including a great unknown.

DR. JOHNSON: But we've got a functional outcome in the core, correct?

DR. GIANNINI: Right.

DR. JOHNSON: So are you proposing that in addition to three-month signs and symptoms via the core, let's say, with caveats for Paucis and polys, that there would be a 12-month pure functional outcome?

DR. PETTY: That's the question I'm asking you.

DR. JOHNSON: Yes. Well, as a pediatric rheumatologist, is that a major impact to the patient, do you think?

DR. PETTY: Sure, it's a major impact, but my question is whether or not we can actually measure it. I mean, one of the things that--we can measure functional

outcomes reasonably well in some circumstances. The question I have, and Lori outlined it very well, but the question I have is, can we actually measure quality of life with any validity at all in this age group? I get the impression that we probably can't. We don't know that we can.

Certainly, my own experience with it is very limited, so I'm not speaking from any authority except from anecdote, which says that the patient's or parent's assessment of quality of life really is defined in terms of what they expect and what they expect varies a great deal from center to center, as has been indicated, and with ethnicity and rural versus urban backgrounds and so on.

It seems to me a much more complicated issue than functional outcome, and I think if we link them, we're going to lose the usefulness of the functional outcome measurement.

DR. JOHNSON: But you don't want to choose an outcome because you've got a measure that you think might work. Evidently, the functional measures seem more developed than the quality of life measures, so from that point of view, you might select that one. But I don't think that that's logical.

I think what you need is to look at the kids and

look at the disease and say, what's major, because it'll fail otherwise, if this is just a trivial thing, or it'll get abused by the drug companies because they'll pursue this outcome because it's easy to achieve and the patients will not have improved. So we've got to set out a relatively high hurdle but not something that's outrageous or totally unreachable and we may need to develop measures to then achieve it.

DR. LOVELL: I think the state of the situation in quality of life instrument isn't as dismal as we might expect. Caren Duffy's tool, I think, has been meticulously developed and he's very far along in the process. He has two subscales, I think, that are giving him some problems now that he's fine tuning. But overall, the validity and reliability of the tools has been well demonstrated and has been very high.

So I think that at least in that instance, with that tool, he's close to being to the point where it would be quite useful, I think, in actual clinical trials, and they've shown because of its design that its sensitivity to change is really very, very good. So it's not that far away from being a useful instrument that has been well validated for JRA patients and normed, also.

DR. JOHNSON: Two more minutes. Any other

comments from the--

DR. WALLACE: I'd like to make a comment about ethics, and this may or may not be an issue and maybe it's already resolved, but I would certainly like to strongly urge that we not do placebo studies. I don't think there's any role for that in JRA.

DR. JOHNSON: We'll come back to that.

Sir? Can you identify yourself, please?

DR. WILSON: Yes. Rich Wilson, Taft Holdings. The background for my question is that I certainly think it's valuable to understand outcomes and health-related quality of life as we can collect valid information. Would those of you who know about this comment on the, I guess I'd call it the attention span that people have in completing these questionnaires, all the way from a couple of questions--we've dealt for this with years in different areas having to do with desiring data in studies, but it's a really good question, so would you please comment on that?

DR. TUCKER: I think the question you're asking obviously refers to what's called respondent burden. Some of the functional status questionnaires that are available are very brief and very easy for parents to fill out in, really, five or ten minutes or even less in a waiting room situation. Some of the longer questionnaires, one of the

difficulties with the quality of life questionnaires that are being developed is because we're not very far along, we haven't gotten to the point where we can drop out questions and make it shorter.

In our clinic, I certainly have to say the patients wait a certain amount of time to see the doctor. They don't generally mind spending ten minutes filling out a questionnaire. There is some learning curve, so that if you're asking people to do it over and over again, they learn how to do it, so when they do it the second and third time, they're faster.

But I think it's an important question, particularly in the context of a big clinical trial, because if you have a multi-center clinical trial, that means different people are administering these in different clinical situations and I think it may be difficult if it's a long and complex questionnaire.

DR. JOHNSON: Yes?

DR. LEIKIN: I'd like to just respond a little bit to your comment about consent forms and so on. I agree with you there. They're much too technical and they're written at too high an educational level and frequently they're mainly to protect the institution and not the patient.

I think they do have the advantage, however, of

getting the physician as they go through the elements of information that are required for the investigator to think about the ethical issues that are involved in the study.

I think the most important thing about the consent process is the oral consent and not the written consent. That's where the payload is, and the most important thing about that is in informing the parent that the investigator has a dual role, that everything that's going to be done for the patient may not necessarily be in their best interest, that the protocol is going to have to be followed for some reason, and even to get them involved, some patient interest may have to be sacrificed.

There is this common therapeutic misconception that people have is that when they go to every doctor, they are going to be treated only for their benefit and they have to understand that the researcher has a conflict of interest. So I think that's the most important thing to be relayed as best as you can.

DR. JOHNSON: A final comment?

MR. DIETZ: I have a two-part question, Dietz Pharmacy and Upjohn. I have a two-part question.

Number one, how stable are these instruments, particularly quality of life, in a population that's changing their social and physiologic, psychologic

background? For example, a 12-year-old may be very immature and as a 13 much more mature. What effect is that going to have on your quality of life?

The second thing is, in the clinical trial, where you are going to be repeating this measure or this instrument over a period of a year or longer, how stable is this instrument in a repeated measures situation, because it will be a repeated measure instrument when you look at it in a clinical trial at three months, six months, nine months, 12 months, whatever.

DR. JOHNSON: You want to handle that one?

DR. TUCKER: Some of that, there's answers to. I think you get to the point of why you have to have norms for each age range, because you're right. Twelve-year-olds, 13-year-olds, 14-year-olds may be different, and as I mentioned in my talk, even amongst 12-year-olds, there may be a very broad range of abilities or difficulties, and I think that's a particular problem inherent with these measurement tools. But I think they really need to be normed on as normal a population as you can and some of the instruments haven't, or there hasn't been adequate data to really help us in that regard.

The second question, about repeated measures, I think some of these functional status tools have been used

in some settings where they've done them over time and they've performed very well. I don't--the person who is working on the JAQQ has also been using that over some period of time to measure responsiveness and it's done a very nice job. The generic portion of the questionnaire that we work on has been used in a couple of populations over some period of time and it's performed pretty well. But we're doing some more research to look into that.

DR. JOHNSON: Okay.

DR. GIANNINI: Related to that, are we considering giving the quality of life six months after the trial is ended? If we have a six-month trial and we're saying that the minimum amount of time might be a year, I can't see that the score you're going to get on the quality of life instruments at the 12-month period is going to reflect what happened in the clinical trial.

DR. JOHNSON: The trial would be 12 months.

DR. LOVELL: It's tough. The way this would work is if you're going for a quality of life claim, you'd have to do a trial of the duration at which you think that you state as the minimum duration. In adults, the quality of life claim has to be 12 months or longer.

DR. JOHNSON: We'll come back to that, because the same issues are going to come up with these other two

claims.

We have to take a break and I think we're going to make it a ten-minute break and try to regain some of our lost time. Thank you very much.

[Recess.]

DR. JOHNSON: Would everybody take their seats, please.

DR. RIDER: We would like people to get back to their seats, please, so we could start the second half of the morning.

MR. MILLER: Would everyone try to return to their seats so that we can begin the next session, please?

DR. JOHNSON: Please take your seats. Would everyone please take their seats. We're behind schedule. We have to move on.

DR. RIDER: We'd like to continue now with consideration of prevention of structural damage as another claim for licensing new agents. We'll begin with a presentation by Dr. Andrew Poznanski.

III. PREVENTION OF STRUCTURAL DAMAGE

DR. POZNANSKI: I'm going to talk today about the use of radiology in all this. Could we dim the lights a little bit, please?

In terms of looking at the outcome radiologically,

I think radiology does have, I think, a useful measure in this, particularly in the Pauciarticular and polyarticular forms, less so in the systemic. However, we have to be sure that we use different radiological criteria than those used for adults. The adult criteria can be used in late teenagers, but in a two- to three-year-old, for example, they're sort of useless.

Some of the things we'll be using are soft tissue swelling, which is not a very strong sign, joint effusion, apparent joint width, which we'll talk about a lot more later, erosions, which are problematic in the very young child, osteopenia, or the thickness of the cortex has some value, joint fusions, and joint dislocations.

Here's an example of a child who had in a period of eight months a tremendous amount of loss of bone. Could we darken this just a little bit more? You can see that the cortex of the second metacarpal, which is easy to measure on all our hand radiographs, has decreased significantly and that this has occurred by endosteo-resorption [ph.]. If we plot this on a graph, you can see that in eight months, the cortical thickness went from here to here, and this is the minus two standard deviation line.

So the hand x-ray gives a nice measure of bone loss or gain and the loss is always by endosteal resorption.

If we see a thin cortex on the outside, it means that there's been lack of bone formation, so it gives you useful information in that aspect, also.

We also have special studies that we can use, and we'll go over those later, the MRI, which allows us to look at cartilage, synovitis, effusion, erosions; bone scintigraphy, which shows joint activity; ultrasound that you can see here in the hip shows joint effusion, some people have used it for cartilage, although it's probably not as sensitive as MR; and thermography, which is not very reliable.

For radiologic evaluation of cartilage, we can do this directly by using MRI or arthroscopy or arthrography, and here is an example of one of the newer sequences that is available for this called a 3-D sequence called spoiled gradient echo, and you can see how sharply you can delineate the cartilage and separate the cartilage from the bone. Really, it looks very much like an anatomical section. Now, this has just become available not too long, so we have not had a great deal of experience with this sequence, but it has been extremely useful for looking in very great detail into the appearance of the cartilage.

Indirectly, we look for apparent joint narrowing, of course, erosion, and abnormally shaped carpals, such as

angular carpals.

Now, you can see with other sequences, which are more readily available, you can also see cartilage. Here, you can see a knee in a child. Here's the epiphysis, but here is the real epiphysis, which is made of cartilage, and here, the tibia, the same thing. You can sometimes separate the difference between the growth cartilage and the articular cartilage. You can see the articular cartilage here is a little brighter along the edge, and here it is on a gradient echo sequence where the cartilage is very white and you can see the same sort of thing.

We mentioned earlier the angular carpals, and when they have little points like this or like that, it usually means that something's going on and there is damage to the cartilage. It's a nice secondary sign. It's hard to quantitate.

What about joint width? In JRA, of course, it's very misleading, because if you look at a joint in a child, you're actually seeing the growth cartilage as well as the articular cartilage, and so the growth width that you see radiographically will be spaced from one epiphysis to the other, which includes a lot more than joint cartilage. You can lose a lot of cartilage and still see a sizeable joint.

On the other hand, in an adult, where all you have

left is the cartilage, a very slight change is easily visible. So this is not easily visible until it gets very marked or until the angular configuration becomes visible.

Also, the apparent narrowing may be due not only to erosion of cartilage but increasing skeletal maturation, so that if a side is more mature than the other, it will look like the joint space is narrower.

Apparent widening of the joint space from effusion, for example, we can see that sometimes in the knee or in the hip, and in the knee, particularly, joint space is a problem because the knee is a relatively lax joint. If you're not taking your films weight-bearing, you can get a marked variation in appearance of the joint width.

Here's a picture from Bywaters which shows essentially the same thing on an anatomical basis, a child who died in an accident. We unfortunately have very little data anatomically on what this looks like, and so a lot of our studies don't have the gold standard to compare to. But here, you can see that there is an irregularity of the cartilage. You can also see this angular appearance of the ossification, which I mentioned before.

Here is a knee in an older child. Of course, here, when a standing knee, you can see that there is no joint and that is not a problem.

So how do we evaluate this apparent joint width? Well, we can use subjective things, just from what you see and experience, comparison of one side to the other, but that only works if one side is involved and the other is not. Comparison to other digits in the hand, if one finger is involved and one is not. Or comparison to bone age books. Here is just a line drawing from an actual x-ray and some bone age images. This child was a two-year-old and with quite a bit of swelling around the knee. You can see that these centers are quite a bit closer together than they are either for the two-year standard or the 11-month standard, although the maturation is even closer to the 11-month standard.

Or you can use objective measurements, which we'll talk about later, which are the radiometacarpal measurements, as well as other measurements that have been obtained. This is the same knee of this child with arthritis and here is the norm. You can also see a little bit of this angular appearance of the basis of the epiphysis, which is a useful sign. These are all signs that you don't see in the adult.

Cartilage can increase in thickness. This is a case I got in Australia. It's an old case, and I don't know what therapy the child had over a period of a number of

years. It's written on the bottom, but some heads are in the way, so I can't see, or something's in the way, but anyhow, it is about a two-year period or so. You can see the joint widened considerably. The problem in these cases, we don't know what the widening is due to, whether it's new growth cartilage, new articular cartilage, or perhaps even fibrocartilage. I think with MR, if we ever did that, we would know some of that information.

The scoring methods that have been used in adults have little value in very young children, because--and, therefore, the erosions are an unreliable sign because you really don't see them except in teenagers. In the late teens, you certainly could use the scoring methods. With thick cartilage, much erosion can occur before it's visible in x-ray. And even if you see progressive erosion on the x-ray, this may not be real because you have maybe just simply ossified cartilage that has already been damaged, so it may be just maturation rather than structure.

So what about some of the measures that are useful? One of the things that's probably most useful is in the hand, and that, of course, will work only if the hand is involved. But what we did is we measured the distance between the third metacarpal here and the epiphysis here, and as you can see, this includes quite a few cartilages all

the way along.

We looked at this in relationship to age, to size, and to the length of the second metacarpal, and the best correlation was with size of metacarpal length rather than age, so we developed our standard in relation to this, to the length of the metacarpal, which actually related very well to stature, as well. The reason for that was that because if a child is very small or very large, obviously the carpus will be smaller or large.

We did develop some knee measures, which we haven't published yet, but the problem there, there's a wide variation and that's because it's not as sensitive probably because the joint is usually taken in a lying down position, and two, you're only measuring two cartilage layers.

And then, of course, you can measure change in inflammatory process or synovitis with MRI and we can use some gadolinium.

Here is how the measures are obtained. We measure from here to here and we are relating it to the length of the second metacarpal, the maximum length of the second metacarpal. We also related it to width, but we used that mainly for metathaseal dysplasia [ph.], physiodysplasia, where often the metacarpals may be short.

Here is a distribution of children with hand

involvement in JRA and you can see that many of them are below the two standard deviation line.

Just how is this used in practice? Here's a child at age two and a half. If you're used to looking at this radiograph in children, you know that this carpus is really too small, but it's really hard to quantitate that unless you do it this way, and at two and a half, this child had a lot of swelling around this joint. You can see this first red point here was where it was, way below the two standard deviation line.

At age five, now we can see that there is abnormality and it had gotten worse, so it went really downhill. But at this place, many people would have missed this as joint involvement, and yet it is a very obvious involvement of that joint.

Another case, a similar sort of thing. Here is a youngster here. Again, the carpus appears small and it's well below the standard two deviation line. However, with therapy, this is how it looks and it's actually following the growth curve. So at least it's not getting worse.

Another case, here's a child's left and a right hand here and you can see the advanced maturation on this side. This is a current case I just had very recently. The carpus, in spite of these carpals being more advanced

looking, looks smaller than the carpus here. As we follow this, this is the same child. This is the same hand as here at plus seven-and-a-half months in this. You can see the advanced maturation and now you can see that there is some disease.

If we look at what happened here, you can see that this child went from here to here in a period of seven-and-a-half months and this was the apparently normal side, which is actually a little low, as well, but had stayed quite constant.

We applied this to a couple of studies. We did some with the Russian penicillin mean study, which had a sort of a null effect, and this may have been because it wasn't getting much result. Also, the timing was relatively short.

We did a recent study using methotrexate and looking at this, and 11 out of 17 responders had improved carpal length after a mean of two and a half years of treatment, so we had a longer treatment period. One of the problems with radiological changes is they do take a little more time to show on the radiographs. All six clinical non-responders have progressive loss. The decrease in carpal size occurred in both responders and non-responders prior to the methotrexate therapy.

Here is basically what it was before treatment on one of the hands. This is the mean for the left hand or right hand--I can't remember; we had separate means--from minus one to minus 2.1 standard deviation and it went up to minus 1.42, while the other one went from 1.24 to minus 2.47 in the non-responder group.

Here is an example of one of the children, one of our better results, and here is the before treatment and here is after treatment. You can see the marked widening of the space between the carpals that has occurred from here to here, and this could be quantitated on the curve.

Here is just an example of two different patients, an example of a responder and a non-responder. You can see the non-responder went sort of like this and then after methotrexate kept on going downhill. The other one went like this before therapy and then with therapy improved. So it gives you a nice objective measure of looking what's happening at the cartilage in the wrist.

The pitfalls of this is that the wrist and metacarpals must be parallel to the film. This is sometimes difficult if there's a contracture. However, by imaging the wrist separately and the metacarpals separately for the length, that can actually be done.

However, also, the carpus can be small for other

reasons. If you damage the growth of the cartilage, of course, that will give you a sign of a small cartilage, but that's probably significant, as well, or if there's an associated dysplasia, which usually we can rule out.

The advantages of it, it's a relatively inexpensive technique. You can use the same x-rays you have for everything else. You don't need an additional image. Usually, you use it for qualitative evaluation. The measurements are most useful in the very young children where the carpals are still mainly carlaginous [ph.], and as I mentioned, the standards are related indirectly to stature.

How about looking at inflammation, synovitis, pannus, so forth? There are several ways of doing it. The x-ray is, of course, not very good at this, but bone scintigraphy will give you some evidence. Probably the best method right now is using MRI with injective contrast, meaning one of the gadolinium compounds, which is probably the method of choice.

Here's a bone scan in a child with JRA. You can see this is a flow study and you can see increased flow to the affected knee here. In the later film, you can actually see some increased activity around the edge of the joint. These are the growth plates. This is tibia, fibula, and

this is the distil femur here. The growth plates normally are hot like this, so this is one of the normal findings in children.

Here is some hand on an older child, and you can see here that the third metacarpal is most affected compared to the second, and on the other side, the second is more affected than the third. If you look at the corresponding x-rays, you see that this joint is narrower than this one and that this joint is narrower than that one. So the joint narrowing here corresponds with that. But otherwise, we found the correspondence wasn't always very good with bone scanning and we felt that the MRI is a better method.

As I mentioned, an MRI, I think the ideal one to look at cartilage is the 3-D spoiled gradient echo--it's called SPGR in the GE system--using fat suppression. The other advantage of this technique is once you've developed this, you can then look at it in any plane that you want because just with the computer you can look at it in AP, lateral, actual, coronal, sagittals, anything you want.

The other system is the multiple radiant echo, which gives you that bright cartilage which I showed you, if this is not available.

However, if you want to look at inflammatory change and synovitis, then we take one T1 weighted before

gadolinium and a T1 fat saturated after gadolinium, which needs to be obtained quickly after injection because the material also eventually goes into the synovial fluid.

This, of course, is useful both in JRA and RA. It's useful in the response to therapy. There was a nice French study that showed this, and it allows more accurate determination of cartilage thickness when you have the contrast, so it's an added benefit that way, as well.

Here is just an example of a child, here before gadolinium. You can see this dark area here, and you can't separate what it is. After injection, you see a little brightness around the edge and you see a lot of high-signal area right here which wasn't there. This corresponds--this is a path specimen from Dr. Milburn's book of a JRA knee, and you can see the invasion of the pannus coming in the back of the knee here, which will correspond very nicely to this. These are obviously different patients, but it gives you the same sort of appearance that you would expect to see there.

This is the same child as the other one, just comparing T1 with the--no, I'm sorry. This is a different child, showing again before gadolinium and after gadolinium. The black area that persists, by the way, is fluid, because the fluid doesn't--initially, it will pass it by. But you

can see, again, a lot of stuff here that's enhancing that was black here.

You can do this in other joints. Here is a knee before and after gadolinium. You see a lot of brightness around here which was not present here. And you can do this in the temporomandibular joints. Here is the mandibular condyle here. Here is the mandibular condyle here, and you can see around the joint, this area now enhances, showing there is an inflammatory process going on in there.

So the advantage of using MRI in JRA, it's the best method of looking at joint erosion, the best method of looking at synovitis, and it's best for looking at C1-C2 involvement in the spine. Here, you can see a little bit of pannus pressing very delicately on the upper cord.

It's also useful, however, to look at joint effusion, subtle bone erosion, ligamentous change, meniscal abnormality, and avascular necrosis. Those can be looked at in different ways, but MR is still a very nice way of doing it.

Here is an old study, so that even with the old MR, you can see this. Here is a child's knee, and we couldn't really see any erosions here, and yet, here you can see them very nicely on just simply T1 studies. So even erosions show up better--subcortical cysts, I should say, in

this case.

We found that menisci get involved in the knee, get abnormal in the knee, and they get a sort of a flattened and irregular shape, and when we plotted, we measured the area of the meniscus in the mid-portion, and the Xs are the JRA meniscus and the dots are the normal controls which we got from children with tumors and other things, you can see that the means are quite set apart and there's a fairly good separation between this group and that, both for the medial and--this is the medial meniscus, but we have similar data on the lateral meniscus.

So in summary, the radiological methods are useful in evaluating outcome of therapy in JRA. The most useful ones probably are the radial metacarpal distance and the MRI with gadolinium. Scoring methods which are based on erosion are useful only after growth has ceased, so they're not very much value. There are many other measures that come in secondarily, as I mentioned, such as effusions, such as just inflammation generally, such as hyperemic changes which occur, and there's lots of these, but these are a little harder to quantitate. I think these would be a useful way of measuring effect of a drug. Thank you.

DR. RIDER: Thank you.

We would next like to hear the prospective of a

pediatric rheumatologist, Dr. Carol Wallace.

DR. WALLACE: I'd like to thank Dr. Poznanski for those wonderful slides and that very important information.

In thinking about radiologic assessment, I think the specifics from Dr. Poznanski were superb, and just some more thoughts about that. I think he gave us great ideas about what should we be quantifying. Some other things to think about are when should we do these quantifications, when should measurements be done, which joints should we look at, and I think he alluded to that in terms of certainly if the wrists are involved versus knees, et cetera, and what's going to be the best imaging study, and I'll sort of recap these.

Despite the fact that it's often hard to evaluate joint space narrowing, I think it is important from the standpoint that if it truly is there, that is the beginning of destruction, and I think in a lot of studies, this has been overlooked and is important. Certainly, erosions we all know about.

I think another important point that Dr. Poznanski pointed out is the difference between are we really seeing, or do we want to think about improvement versus lack of progression, and we may actually have lack of progression when, in fact, we think we have worsening, i.e., the going

from a carlaginous stage to the bony stage and now having an erosion which "wasn't there", and that's a problem with plain films versus MRI.

Then another issue that I often struggle with with the more advanced patients are those trying to get radiologists to help us figure out what is the difference between inflammatory changes versus those degenerative changes that go on in a severely involved joint where maybe there truly is no longer any inflammation but there's been so much damage that now you get progression of degenerative changes.

I think this is what we'd all love to see in all of our patients, the wrist on the left, and then after months and months of therapy, much improved wrist on the right. But how do you describe that? How do you quantify that? That's what the crux of our problem is.

One of the critical issues is when are we going to do assessments. Typically, we do them at the start of treatment. I think it's also important to do it at the time of response, or maybe it's more important to do it at the time of maximal response, and then to look at a time period after that, be that months and probably most often years.

But if we just wait and do it at the start of treatment and then at the end, the top and the bottom, we

really miss a lot of important information because there's a lot of damage that continues to go on until you get at that point, which hopefully, or may be remission or at least maximal response. So the critical time is actually, I think, going to be between those last two measurements in terms of a candidate drug making a claim about lack of x-ray progression or even improvement.

If we look historically, if we go to the literature to see what does the literature say about timing, it doesn't give us much help. When we look at Dr. Poznanski's study with Havel, et al, the patients were treated with methotrexate for at least 12 months and they showed wonderful improvement in carpal length, but one of the problems was is the patients actually had infrequent x-rays. What was said was that there was a mean time of x-ray at 2.5 years, but we really don't know the range. We really don't know whether they had serial x-rays and sort of what happened along the way.

Likewise, in a study by Bianca Lang, et al, in 1995, again, a very useful and important article looking at systemic JRA, and basically, it was a catalog of findings. What we found was certainly erosions, which we all know about, that occur within two years, 31 percent, subchondral irregularities, ankylosis, subluxation, but problems were

that, again, they were sort of random x-rays and not serial, not at set times where we could sort of make sense out of what went on, and the follow-up was anywhere from one month to 11 years, which is quite a long range of time. Although the data was there, they didn't make it very clear as to what went on within the first year of disease in those patients.

Maybe a little bit more information could be gotten from Joe Levisson's patients in Cincinnati, along with Ed Giannini, I know, helped out with this, and Dan Lovell, and many of you have seen this slide before. What this was was a group of 117 patients with JRA who were followed serially from the beginning. They were seen for disease onset within the first six months and then they had x-rays at every six months and then these were looked at. The joint damage included joint space narrowing, erosions, et cetera.

You can see sort of the difference by disease onset type of when--and this was the median time, not the mean, the median time of joint damage. So what that tells us is that if we're going to use joints, at least with conventional x-rays in terms of candidate claim for medications, we're looking at a long time period. Certainly with MRI, that's going to be very different.

So now, then, going back and looking at--if we're going to include joints, which joints are we going to image? I think that the temporomandibular joints are exquisitely sensitive to damage, and if we use those, by the time we recognize anything is going on, most of them have already been damaged, so I think that's actually probably too sensitive for our use in studies.

Wrists, I think, are quite excellent if, indeed, they're involved. Fingers and toes are superb. Hips maybe take longer, but maybe in systemics, actually, hips almost seem to be a target joint. Certainly knees seem to take longer, but on the other hand, if we're able to have MRI data, that certainly could change that completely.

So in thinking about the use of radiologic assessment, is it useful for drug trials? I think, certainly for entry criteria, we should definitely think about it, stratifying patients, those who have known changes versus those that don't, or certain drug trials with only those patients who already are known to have damage or suspected damage, et cetera.

If we're going to use radiologic assessment for outcome, if we're using traditional radiographs, I think that there's no point in using it for any trial under two years. However, if we're going to be looking at remittive

agents and long-term trials, I think absolutely.

But I think the most exciting thing is the possibility of using MRI to really look carefully at joints, and I think with the MRI, we're going to be surprised at the awful things we're going to see, but I think we need to look anyway.

And I think with the MRI, although it's going to be ideal, we're going to see a lot of abnormalities that we don't know yet what to make sense of it, and I think that doesn't mean we shouldn't look, and I think we should, but I think, then, we can use it to look at, do these alterations halt? Do they heal? Do they progress? What happens from there?

So this is just a very brief look-see to actually stimulate discussion.

DR. RIDER: Thank you very much.

I'd like to next hear from our critical commentators to see if they have any comments on these presentations.

CRITICAL RESPONSE/GENERAL DISCUSSION

DR. ATHREYA: Yes. Just like with Dr. Baldee, timed measurements, maybe we need to think about from a time point of view, also, two to six months, six to one year, and maybe some overlaps, and in the earlier ones, we could be

measuring blood flow.

I just have this power doppler, which does pretty good with the--I mean, it's still in development, I think, at the University of Michigan. I've seen some pictures from them. They're also, I think, trying it on adults with osteoarthritis, I think.

So blood flow, and then the synovial thing with MRI. And the cartilage, even some of the newer modalities even show water changes in the cartilage, from what I know. So maybe those are the kind of things we should use earlier and then later on we can use the traditional ones, and even MRI. But then the problem would be the cost and some of the younger ones, putting them to sleep and keeping them quiet and all those things.

DR. RIDER: Any other comments from the critical commentators?

[No response.]

DR. RIDER: Then I'd like to open this for general discussion. I'd first like to begin by asking Dr. Poznanski about the sensitivity to change and the reliability of the cortical thickness measurements as well as the metacarpal measurements.

DR. POZNANSKI: In terms of--the cortical measurements have been around for a long time. They have

been sort of abandoned by the adult people and they're using DEXA. We have both DEXA and cortical measurements in our place and we use them both.

But I think that in many of these cases, if you use a special magnifying glass and you have high-resolution films, and this, incidentally, you should do for any cases of hand x-rays. We're using mammography film for all our hand x-rays because it does pick out some of these finer details that you will miss otherwise. It does add a little bit of radiation, but in the hand, it's really not a particularly risky area to do it and it's not that much anymore. In the old days, we had to use industrial film, which added quite a bit of radiation.

But there have been a number of studies that have shown the sensitivity and specificity of this over the years, so this is nothing really new. It's just that it's been abandoned for a while.

But I think in pediatrics, the advantage is that they often lose a lot of bone on the inside of the bone and osteoresorption. That very quickly, as you saw in that child that I showed you, it went like about a four standard deviation leap in about eight months, so it's a pretty sensitive method.

DR. RIDER: Do you think both these methods would

be sensitive for trials of one year in duration?

DR. POZNANSKI: Oh, absolutely, for that. That would be sensitive.

One other comment I just wanted to make about MRI, which you alluded to, is the problem with the children under six years, where really you have to sedate them. So it's not only the cost. It is the added risk. In our institution, like man children's hospitals, where you have proper care, you can control this very well. We have nurses there and we very carefully monitor all our patients during sedation. But it is, nevertheless, a risk when you sedate a child, even with the benign--relatively benign--sedating agents.

Somebody brought up TMJs. If you're going to look at TMJs, really, the only way to look at them is with MR because you can miss the early changes on plain film very, very easily. But otherwise, MRI for acute disease is really the way to go, absolutely, because you can see it, and the Paris study, where they actually injected the stuff into the joint, showed a very short-term response to the steroids and a marked decrease on the MRI. So it was a very pretty study.

DR. JOHNSON: It sounds like we're going to need some open studies anyway to see what all these sensitive

changes really mean clinically. I mean, it doesn't sound like there's going to be a limitation in the technology to show something involving the structure of the joint that one could argue is important.

But if you have one year or two year data to show that it has clinical ramification and improves the plain film, let's say, then we're back to the same question as to what duration of a trial would one like to see to do justice to the claim of structural retardation, we're calling it. With the MRI, you can probably show changes in a month, but I presume that people would think that a one month trial is not very meaningful.

DR. POZNANSKI: But you also could see changes in cartilage, which are longer-term changes, so you see both. In other words, with MRI, you see the acute thing if you give gadolinium and you see the structural changes, anatomical changes, which can take longer at any time. So you're talking about two different types of MRI, two different ways of doing it.

DR. JOHNSON: Right, but I don't think anybody is proposing, at least in the JRA world, to give a claim for structural retardation alone. That issue has come up in osteoarthritis in the adult world. What do we do with a drug that stops the x-ray progression but does nothing

clinically over a year's time? I mean, that's sort of a tough issue.

But here, if we link this to improvement by signs and symptoms, what duration of structural change is important clinically? I think that's the question we need to try to grapple with, one of them.

DR. WALLACE: It seems to me from what Dr. Poznanski has presented with the wrist, if we were to use that model, that it would be--I think a year would make sense. Certainly, if we're not using the wrist, if we're using other joints, probably more than a year, one would have to--

DR. JOHNSON: But again, that's reasoning driven by the characteristics of the measures.

DR. WALLACE: Right.

DR. JOHNSON: What we also need is reasoning driven by the characteristics of the disease. Maybe it should be five years. That's probably ridiculous, but it surely shouldn't be five months, probably. There's got to be some decision halfway in between.

With the two-and-a-half year, methotrexate, did you have interim x-rays and nothing happened over a year's time?

DR. POZNANSKI: I'll tell you, that was sort of a

retrospective study, basically. That's the problem. Some of the cases, we had a lot of x-rays. This was a group of children who were treated at Larabeta Hospital [ph.]. So some of them had a lot, and we measured actually all of them, all the x-rays that they had. So there were also some different intervals, and that's what you alluded to. There were some long-term treatments, some short-term--

DR. WALLACE: Sure, and I think--

DR. POZNANSKI: It was not a consistent--

DR. JOHNSON: We could start some open studies to look at that--

DR. POZNANSKI: So it was not an ideal study. If somebody did consistent six-month x-rays, it would have been, obviously, much better.

DR. WALLACE: But I think that was Ed and Dan's data, was that. Those were done every six months.

DR. GIANNINI: Let me ask a question about that. When we published that, we took some flack for doing films that frequently. Let me ask what the--using modern-day technology, what's the feeling as to how frequently you can do a panel of films like that on a kid?

DR. POZNANSKI: As far as the x-rays of the hand, you could really do them six months, or even daily, almost, without--I mean, it's a non--the effective dose equivalent

to the body would be very, very small with that. There's not very much bone marrow, and so the risk--it's not even included in the risk figures by the ICR, BRNCRP, what--

DR. JOHNSON: But can you convince parents of that and is it going to cut into you are cruel? That's the issue, isn't it?

DR. POZNANSKI: Obviously, some parents are very sensitive anyhow, but with explanation, the x-rays to the hand--it's a relatively low-dose study, even with the mammography film, and it is not particularly a risk.

Of course, if you're going to do hips, that's a different story. That would be more of a problem, because you're starting to get into areas, A) where there's more bone marrow, and B) where there's gonads, so that people are sensitive to that.

The knees would be not too bad, but it's quite a bit more radiation to do a knee than a hand x-ray, for example, because the thinner the part, the less x-ray you need to radiograph it.

DR. GIANNINI: So what would get by in IRB these days?

DR. POZNANSKI: I don't think anybody would have any problem with six-month studies, because, I mean, that's just from a management point.

DR. STRAND: I'm a little puzzled about why you're suggesting open studies. For instance, we've had this goal for x-ray for adult RA for a long time and no product has yet met that goal, yet we very readily agree that we should be looking for that kind of a claim as an iterative claim on top of signs and symptoms and that we needed 12-month data.

I mean, a similar kind of response to the discussion right before the break in terms of disease specific and generic instruments of health-related quality of life and function. Functional instruments are much better well developed in adult disease, as well, and the health-related quality of life is still fairly new to be measured, although we have instruments, perhaps, that are a little further along.

It seems to me that we have to do these studies and that we're looking at new therapeutic interventions that we're simply going to have to do x-ray and MRI, as appropriate, and health-related quality of life with function, as appropriate, and validate them in that context, and to do it in an open study isn't going to really help us very much.

DR. JOHNSON: I don't think that's entirely true. What I'm interested in is what does an x-ray mean in terms of a risk factor for downstream disability, and you can

ascertain that epidemiologically. If there were a strong association, like between hypertension and strokes, then the clinical hurdle is going to be less and we would be more prone to look at a claim that retarded x-rays as able to stand in and of itself. I think that's the only difference.

It's the same in the OA world. They're trying to correlate joint space narrowing in the knee with long-term clinical disability, and--

DR. STRAND: That isn't affected in this study, and I agree, that would have to be open label. But it seems to me that doesn't prevent us still from doing--putting these instruments into our current clinical trials and see what the shortest possible interval is to see difference. I mean, we were even arguing that the SF-36 could show a change in less than six months, and certainly we know that the HAQ and the MACTAR and all of those can, the AIMS, too, and I think you also believe the JAFAR and the JAQQ, et cetera, show changes in shorter periods of time.

DR. SUNDELL: I think that one of the things we wrestle with is whether x-ray changes are an outcome or a marker. Are they in and of themselves unsatisfactory and should be an endpoint for this trial, or do they indicate down the road that there will be problems? I don't think we know enough to answer those questions, but I think those of

us who take care of patients regard them as both, that if we see x-ray changes, we know that we are not succeeding.

Although the literature documents a discrepancy between clinical manifestations and x-ray changes, such that children may be utterly asymptomatic but have progression of x-ray changes, I think, nonetheless, one of the things that clinicians do use is evidence of x-ray progression to indicate that our treatments are not satisfactory and I think that, long-term, the problems that these patients get, such as the systemics with hip problems, are indeed manifested by these x-ray changes.

DR. SILVERMAN: I have a question for Dr. Poznanski. The specificity of gadolinium for active synovitis, I know we've tried some and I've questioned really how specific, not that there isn't enlarged synovium, but has that been really well looked at that it really shows truly active synovitis?

DR. POZNANSKI: The problem with that is the only way to do it is to biopsy all these kids and nobody really wants you to do that. That's a problem we have in a lot of other areas in JRA, is that we have very little pathological material, and without knowing on biopsy what--right now, we assume that this is the gold standard, that gadolinium is the gold standard, but we have no proof for it. There are

some rat studies I suppose you could do to see. That's not exactly the same model, but it's not a bad model, and I don't know if anybody's done that.

DR. SILVERMAN: That was my question, even in animals, where you can get the pathology. I don't think there's any studies, though, to--

DR. POZNANSKI: I don't know.

DR. SILVERMAN: I mean, the thing that had struck me about MR is potentially its over-sensitivity, the ability to see things and then ask the question, what does it mean, and I wonder if gadolinium synovitis may be another one of those--

DR. POZNANSKI: Gadolinium basically is pretty non-specific. It shows you increased flow through those tissues, and so that it does show you, because that is real. The question is, what does that flow mean? Hyperemia, some other kind could do that, conceivably, although this is specific to one localized area, not the other tissues around it. So there is evidence that there is extra flow through the tissues around the edge of the joint, so that that is very suspicious that that would be so. I think it would be interesting to do the studies and--

DR. LOVELL: Earl, I have the same concern you do. MRI in other anatomical sites has resulted in some faults,

indicators of problems, like bulging disk in the spine. We are in the process of doing a study where we are comparing longitudinally in early onset JRA patients, MRI versus standard x-rays in the knees.

The two goals of that study are to try to see if gadolinium actually does increase the predictive value of this MRI scan, and two, to try to figure out which parameters that you get, piece of information you get on the MRI are predictive of changes in the knee x-ray on plain radiograph.

It's a study that we're starting now. It's going to be a longitudinal study and it's going to be of two years' duration in each patient. So hopefully, we'll address some of these issues, but we're just now starting that study.

DR. WALLACE: I was going to ask Dr. Poznanski if when patients have been given gadolinium for other reasons and had an MRI, did the MRI camera kind of just happen to go down over a few joints to see if--in non-JRA patients--to see--

DR. POZNANSKI: Oh, yes. I mean, we do joint areas for tumor, for example.

DR. WALLACE: Right.

DR. POZNANSKI: So we've done it for trauma and

for various other things. You get a very minimal enhancement of the synovium normally, so we do know what the normal enhancement. There's no question, there is some, because it is a vascular structure.

DR. WALLACE: Sure.

DR. POZNANSKI: But we can usually separate it from the very severe that we've seen in these cases that I showed you, which is a much marked--you get a very faint rim of increased activity around the normal joint if you--

DR. WALLACE: Okay. That's great.

DR. POZNANSKI: But that does occur, yes, and we've seen that. We do more MRI for non-joint things than for joint things.

DR. KATONA: Also, I have a question for Dr. Poznanski. In different institutions, we wrestle with the problem that our radiologists just do not have a whole lot of experience with joint MRIs. What is your feeling what would be the reliability or differences evaluating the MRIs?

DR. POZNANSKI: I think if the technique was done properly, it could be done in a central area, for example. As long as the technique was followed, it's a pretty straightforward thing. If you inject the gadolinium and you take your image immediately afterwards, then you could look at the images and do it. It's not that--

DR. KATONA: But you would have to evaluate it--

DR. POZNANSKI: There would be an advantage if people aren't used to evaluating it, yes, but that should not be a problem. You should be able to do it, if you get adequate studies.

The bigger problem is that, in adult institutions, at least, people are not used to imaging children and they have problems with immobilization and various other things, so we often get moving pictures and various things like that and that is a bigger problem in that people who aren't used to dealing with children. But once you have somebody who can deal with doing the MRI in children and do the technique, they should have no problem producing decent images.

DR. RIDER: Are there any further questions on this subject?

DR. LINDSLEY: I had a question. Again, Andy, with regards to the radiometacarpal measurements, how responsive is that measurement? You showed a couple of examples where the values had returned to the normal range, but were those exceptions? Did you see that very often?

DR. POZNANSKI: No. We haven't done this on a very large scale. The only large study we did was in the Russian study, which we didn't see any results, and then

this study with Dr. Havel. We have not done anything on a large--it's sort of been an ad hoc thing, but we've seen quite a few. I mean, this is not just the unique one or two cases. How many, I don't know. We have not done it in a systematic way. It's just a tool that is a simple tool to use. Anybody can actually do the measurements. It's not that hard. You just need to look at how it was done. The charts are there, so it's pretty straightforward. The main problem you have to worry about is make sure the hand is flat when yo do the x-rays.

DR. RIDER: Thank you.

We'd like to end the morning session with a discussion of remission as an ultimate hurdle for clinical trials, presented by Dr. Carol Wallace.

IV. REMISSION

DR. WALLACE: Actually, I'm going to keep my comments brief because I'd like to have a lot of discussion because I think this is a topic that deserves a lot of discussion.

I think there's no question that all of us would agree that our treatment goals for juvenile rheumatoid arthritis is, first off, prevention of joint damage, next, for return to normal function of our patients, and for normal growth and development. Basically, what we're

talking about is remission, remission meaning no disease.

An important aspect of remission is are we talking about remission on medication or versus off medication, and we can get to that point. But I think more importantly, a lot of people when I talk about remission have said, well, why bother to define it? Why? And then if we are going to define it, how are we going to define it? I think we need to agree on that.

So some thoughts are, why define remission? I think it's terribly important that we have a goal or aim of treatment, and not just for the drug trials but for taking care of the patients. Better, improved, doing well, stable--none of those are good enough. I think we need to treat for remission.

The next is for communication in teaching between ourselves, et cetera. I will go into that.

Next is so we can identify and recognize when we do, in fact, have a superior treatment.

I think remission as a goal, when we talk about some of the disadvantages, the major disadvantage is that some or many, depending on who you talk to, of our patients don't achieve it. Some people feel that this is a reason we should not even use remission as a goal. Another disadvantage is that it's difficult to maintain off of

medications.

Advantages, however, for remission as a goal is that I think it does promote more aggressive treatment, and then remission, even on medications, is definitely healthier for the patients' joints than active disease. So even though patients may not be able to go off all medications, the fact that they've had a time period in remission, whatever our definition of that might be, is definitely healthier for them and their joints.

Looking at the role of communication in terms of having a definition of remission, I think it's terribly important when we communicate among physicians, among family practitioners, among our pediatrician colleagues, internists, adult rheumatologists, et cetera, et cetera, orthopedists, many of whom feel that if a patient gets a little bit better, that's just fine.

Certainly, in teaching residents, it's terribly important that we have a good definition of what we're trying to do for our patients. Certainly with health care providers, governmental agencies, action and support groups; certainly the insurers, and the community at large, I think, understanding what we're trying to do for the treatment of childhood arthritis is going to benefit our patients in the long run if we can communicate it to all of these different

segments of society.

Is there a role for remission in drug trials? I think so. If we're able to define remission, then certainly it will help to identify superior agents, and also, hopefully, will help us search for remittive agents.

Here is a proposal for definition I'd like to put forth and that I'm hoping this will engender a lot of discussion. I think two consecutive months where a patient has less than 15 minutes of morning stiffness, where there's no joint pain and there's no joint swelling. This is obviously based on the adult criteria for remission.

I have left out of here the laboratory parameters. One could add in that if the laboratory parameters were abnormal at the start of the disease, then they could be included for the definition of remission, but since so many of our patients don't have abnormal laboratory parameters, then one doesn't necessarily need that in the basic definition. There are certainly other aspects that we can put in there, as well.

Some people have brought up the idea, is this going to be on medication or off medication? I think we should have a definition of remission on medication and a definition of remission off medication.

Another person brought up the point, well, maybe

we should do synovial biopsies to truly prove that the synovium is not active, because we've all had that unfortunate experience of thinking a patient is in remission and yet having progression of the x-rays, et cetera.

So I would like to open this up, if that's okay, Kent, and get thoughts.

DR. RIDER: Our critical commentators first, please. Dr. Cassidy, do you have a comment?

CRITICAL RESPONSE/GENERAL DISCUSSION

DR. CASSIDY: I think that Dr. Poznanski made a very telling case for introduction of MRI into our evaluation system, and to come back to some of Dr. Lindsley's earlier comments today, in monarticular or oligoarticular disease, it seems to me that this is an ideal way to evaluate what our drugs are doing. It seems to have the sensitivity and the specificity. I don't know about polyarticular disease. It seems to me that would be a much larger problem.

DR. PETTY: I would argue, Carol, that perhaps two months is too short by several months, if one is looking at a remission, just knowing the natural history of the disease and the way even our best patients in terms of response behave, and I would think that--I would suggest six months would be more logical.

DR. WHITE: I agree with you. I think you should go for remission. That's a great goal and it makes us all work a lot harder than we would have, and I think that's your point and I think that's very, very important. As a place to go, I think that's where we should be going.

But I agree. The length of time is really the debate here, and that's a tough one. I don't know if there's a right one. So then you just sort of, you know, like you did, put it up on the screen and let us all shoot at it.

DR. WALLACE: That's fine.

DR. WHITE: Clearly, it's going to differ for the groups that you're looking at, and I think that's what's hard. For me, this discussion comes down to we're talking about very different diseases and we may have to have many more different kinds of definitions.

DR. MAGILAVY: Carol, I question your goal of remission while on continuous therapy, I think especially with new biologics, where the toxicities maybe are not well defined. Clearly, the risk may be much greater than being in remission from disease.

DR. SILVERMAN: Along those lines, I was going to suggest that if you're going to have remission on an agent and as your goal that one should introduce a toxicity

index--

DR. MAGILAVY: Absolutely.

DR. SILVERMAN: --which is actually now being developed. If that were the goal of any therapy without a toxicity index, I think you're going to be in big trouble.

DR. MAGILAVY: Yes.

DR. WALLACE: I think certainly six months is fine with me in terms of remission of disease, but how many biologic agents are you going to be on for six months? This may not apply for biologic agents. Most of the--

MR. MILLER: Or even with the small molecules, it may be the same.

DR. JOHNSON: No. I mean, with the caveat that one addresses safety in some fashion or toxicity in some fashion, why shouldn't it apply? You're talking about the disease, not the intervention. I suppose if it's asymptomatic off-treatment, are you going to call it a cure?

When this came up in the adult world, the issue was brought up about patients who have degenerative fixed deformities and are they ever going to achieve this. There pretty much was a sense in the adult world that they probably wouldn't achieve the adult definition of remission and we're working on some alternative so that those patients don't get ignored.

I don't know what you would do in an issue like this. You don't have function up there, for instance, and what if they had a degenerative need due to longstanding synovitis and still limp? Are they in remission by your criteria?

DR. WALLACE: I think they could be. Yes. So that's why I took it out.

DR. JOHNSON: Should they be? Should you use remission to describe that, or should we use some other term for it, like a fabulous response or something?

DR. WALLACE: You could also put "normal function in non-destroyed joints". You can add on. I think what's up there is the bare minimum, and--

DR. JOHNSON: Normal function in non-destroyed joints, yes, but then you'd have to sort of try to define those things.

DR. WALLACE: That's right.

DR. JOHNSON: I'm just playing the devil's advocate here.

DR. WALLACE: Sure. I think even going for what was up there is going to be pretty tough, but six months is fine by me.

DR. ATHREYA: Six months after stopping the medication, or--

DR. WALLACE: No. No. No. I think we need remission on medicine and then remission off medicine, I think.

DR. ATHREYA: Right.

DR. WALLACE: And the time period doesn't matter to me. I just want a definition.

DR. ATHREYA: By definition, I think remission can be with or without a drug, but I wonder whether for this purpose we should have different words. And actually, I was looking at--since you didn't mention it, maybe I will. The paper from Andersson Gare, she gives some ideas based on the ULAR agreement, at least.

Whether we agree or not, maybe you can see what it is and comment on that since you have that, as another point of discussion. No active synovitis, no extra-articular features, normal acute phase without drugs and less than two years inactive and if it's more than two years, call it remission. That's at least one idea the European group is using, obviously.

DR. WALLACE: Right. I think that's an excellent idea, but I think in this country, inactive carries so much baggage. I have been sent so many inactive patients that still clearly have active disease that I just--you know, maybe we need to develop a totally new word that has no

previous baggage.

DR. KATONA: Carol, what about another wording for remission on drugs, satisfactory control, what the adult rheumatologists use, because basically, the disease is not gone. The disease is still active, just like I think we all know and Balu mentioned earlier, that you discontinue the methotrexate and in most of the cases, the disease is back. So I really have a problem with the remission. Remission means that the disease is gone with no medication.

DR. JOHNSON: You don't know the disease is still there, though. I mean, if you say that your blood tests have to be normal and you can't have extra-articular disease and your x-rays can't have changed, what evidence do you have that there is ongoing disease?

DR. KATONA: You don't, but on the other hand, you do not have evidence the other way, either. The only way you will, when you discontinue the drug.

DR. ATHREYA: See, there are so many patients where you can fulfill those criteria, so you stop the methotrexate and anywhere from two weeks to six months, they're burning up again. So obviously, we didn't really eliminate the disease.

DR. JOHNSON: In the adult world, in DMARD trials, I can only recall one patient out of about 500 or whatever

that went into remission. Of all the pediatric trials, how many would have fulfilled this criteria, do you think?

DR. GIANNINI: Not many. You mean Andersson Gare's?

DR. JOHNSON: No. No. Carol's list.

DR. GIANNINI: To tell you the truth, I don't know, but there's not many. There were some, because we were asked by the sponsoring drug companies to tell us how many there were in remission, what we could consider remission, but not--

DR. JOHNSON: See, there's two parts to this discussion, really. You could conjure up any kind of definition of remission you like and if you make it too lose, then you're going to have placebo patients and naprosyn patients and everybody else getting up into that group. When you do a trial, you're going to always have a control to deal with this issue, but you'll just sort of engender foolishness, because we want the claim to be intrinsically demanding, I think, or else it's sort of pointless and we're going to shoot ourselves in the foot because everybody's going to be going after remission claims and the advance in drug therapy is going to be minimal.

DR. ATHREYA: Isn't that the reason, then, to don't call it real remission? Say this is a good control on

drug, but it does not necessarily mean remission because when you take it out, it's coming back.

DR. JOHNSON: Actually, I'm not even quite--I don't care as much what we call it as to what its criteria are.

DR. WALLACE: So, Balu, why can't we call it remission on drug?

DR. ATHREYA: Yes. That's fine. Something differentiated.

DR. WALLACE: Because I think if we use a word less than remission, I think we're going to get people who still have--if you were to examine him, you'd say, well, this patient still has active disease. I think the words "control", I think the words "stable", I think the words "inactive" are not parallel to what we're looking for. I really don't think they are.

DR. TUCKER: The only thing I would sort of point out is that patients, or consumers, parents or whatever, are going to look for these definitions. I know I have the experience if you say to the parent, remission on drug, remission without drug, they don't hear that second sort of half of things. So for us, you're right. We can distinguish between those things. For the consumer, it may be a tricky concept to distinguish between those two things

and having different words may be more useful.

DR. JOHNSON: It's like in cancer. In oncology, you may need maintenance therapy. It's analogous in that regard.

DR. LINDSLEY: Lori, I really agree with you and I think there is a downside to having the criteria be too short time-wise, because I think that just what you described engenders a lot of false hope sometimes. It engenders noncompliance and a lot of other things that we don't want.

DR. RIDER: What duration of time would you propose?

DR. LINDSLEY: So I would say it's six months--

DR. WALLACE: Great. Let's change it to six months. What about the other things? What about morning stiffness, less than 15 minutes, what about no joint pain, and what about no joint swelling? That's going to be tough for hips, obviously, and shoulders. I left those out.

DR. JOHNSON: It's going to be tough for anybody with preexistent substantial degenerative disease, and maybe we can't include them. That's really the position we ended up taking in the adult world.

DR. WALLACE: Sure. We could have addendums for that and we can have addendums for those with abnormal

laboratory values, as well.

DR. JOHNSON: Well, yes, but you don't want to undermine the credibility of your definition. I think you can't avoiding requiring normal labs, requiring--I would have thought you'd have to have normal extra-articular activity, too, unless we're talking about articular remission and not eye remission. I mean, that would probably do the community a disservice, if we had a remitting agent just for the joints and didn't address the eyes or the fever or this or that. I think you have to make it a pretty pervasive, all-encompassing notion. No progression on the x-rays if we have measures that are credible. That's my opinion. Sir?

DR. RICH WILSON: Rich Wilson, Tap Holdings. I just want to support the general concept of shooting for a high target, such as you've just established. I don't know what the right term or the definition is.

Just to give an example, in the area of hyperreactive airway disease, I think a number of folks around the world were involved with this, but Dr. Ann Wilcock in Sydney, Australia, essentially insisted upon, with appropriate use of steroids, peak flow meters, and other medications, that people with hyperreactive airway disease not just get a little bit better and sort of be kept

out of the hospital but that with very appropriate monitoring and therapy, and this was, of course, by and large on drugs, as needed, inhaled steroids, that their hyperreactive airways could be brought to a point where they could have a normal life.

So that's just by example in a related area of supporting your concept. The definitions, I can't comment on.

DR. GIANNINI: Kent, I have two remarks.

Carol, in your definition, you have two parameters there that are rather subjective and sometimes can be tough to measure in younger kids, the duration of morning stiffness and the joint pain, while Andersson Gare's are a little bit more objective. That's the one remark.

The other remark is I like definitions that don't include physician behavior in them, such as "requires no medication", because the attitudes differ so much. So I would argue for something like Andersson Gare's, where there is a minimum input in terms of physician behavior and that the parameters are objective rather than subjective.

DR. HEPBURN: I would just like to support the feeling that we have to keep the goal high and use a rigorous definition here. I was concerned in the adult session where we began to soften the definition of remission

to the point even where some swollen joints might be accepted in the definition of remission, just because not enough people could possibly meet the definition. That doesn't mean we shouldn't use the definition.

I think, inherently, we all have some concept of what no disease or no active disease is. The oncologists seem to know what that is. I think we have to match this and get the goal out there that somehow we have to try to achieve this. What you do with the inactive partially damaged joints remains an issue, but I think to require no evidence of active disease is important to the definition.

DR. RIDER: Chris?

DR. WILSON: Yes. I just want to--I mean, I agree completely. How can you call it remission if there's detectable disease? It's not a remission. It has to be no detectable disease. I think that's the best criteria.

Secondly, it strikes me as odd with trials that have been done and the accumulated experience of the people around the table that you must not have some idea of how long a remission is likely to be meaningful. It seems to me that some sort of data ought to be available on that, if one goes back and looks at the data that has been collected in other studies with your best available agents or best available programs. What are you achieving in your best

outcome patients?

DR. PETTY: That's a good point, and I think that again points out the fact that we're not dealing with a single disease. Most of us would agree that our polyarticulars, particularly the rheumatoid ones, tend not to remit, and if anything makes them remit, six months would be great. Two years would be better.

If you look at oligoarticulars, again, you will find many of them go on for several years on no drugs and then out of the blue relapse, have a second episode--I don't know what the right term is--sometimes as long as a decade after the last time that they have had active disease. So the individual disease-specific behaviors very much modify the meaning of any duration that we choose.

DR. WILSON: Sure, but you've got them broken down into three groups already, and you've told me, in fact, that you can define some criteria for the two groups. You would say that even a short period of remission in a poly would be more meaningful than a relatively more protracted one in a Pauci. So can you not define some reasonable criteria, recognizing that with Paucis, you may include some individuals that would later relapse anyway.

That's true in oncology jargon, as well. You're not calling these patients cured. You're just saying that

they're in a remission that would not be likely achieved in the absence of therapy in the majority of patients, or in the vast majority.

DR. PETTY: And the number we've bandied about is six months.

DR. WALLACE: Sure. I would go for six months, but on medication. I think six months off medication is a totally different kettle of fish, and I think what we're looking at here is to get a start on things. So six months on medication is fine.

DR. RIDER: I'd like to follow up Ross's and Chris's point that you're beginning to realize that there are some stratification variables that might need to be necessary for these type of trials, and would people like to comment on that further, for example, HLA types, platelet counts in systemic JRA, erosive disease in poly JRA? Would people comment on this?

DR. BOWYER: I'm talking about that this afternoon.

DR. RIDER: Okay. Then from the floor?

MR. LACHENBRUCH: Lachenbruch, FDA. One of the concerns that I've been thinking about, where you're talking about remissions, where you're saying these are likely to be very rare, would make it almost impossible for any drug to

be approved on a remission criteria. Perhaps one way of looking at it is scoring some way of a partial remission in terms of the numbers of symptoms which met this criteria. So I'd like to hear the panel's comments on this.

DR. LOVELL: Actually, I think that's what Ed was going at when he came up with his dichotomous variables of improved or not improved, that you could look at that as kind of a partial remission, if you would.

Getting back to the disease differs--the behavior of the disease differs very much from Pauci to, say, poly, for example, but I don't know if the definition of remission needs to be all that different. No active disease could be defined the same way. The behavior of the population throughout the course of time will obviously be different, but I'm not sure if the definition per se has to be different.

FLOOR COMMENT: Several people mentioned oncology, and previously, I've been involved in oncology drug trials, and they have a number of criteria response to treatment: A complete response, which is the complete disappearance of the disease; a partial response, which is 50 percent reduction in the disease; a stable disease patient who maintains their baseline tumor size, or disease activity, if you will; and those that progress on treatment. Then after

they have finished their course of chemotherapy, if they have had a complete response, then they start talking about remission in terms of the duration of the remission, duration of response. How long were they tumor-free before it came back?

MR. LIPNICK: Bob Lipnick, Washington, D.C. Carol, I think it's really a laudable goal for all of us to go after remission, but I think that it would be inappropriate to water down the definition. The idea--I like what Lori said about patients, consumers, and most of us, when we think of remission--when I think of remission, whether it's stopping a non-steroidal, methotrexate, whatever the medications are, it's stopping and not having recurrence of disease. I think that that's real important that we maintain that.

Does that have to be the goal of a drug study of either--I agree with one of the previous commenters that maybe some gradation of how we interpret the results of our drug studies, because if we are true to form and say you stop the medication and there's no articular activity, and if you have the systemics, there's no extra-articular activity, that that's--it's not going to be achieved by a lot of our patients. But I think that's not to say that certain drugs aren't very useful that we may come across in

a patient.

So I think there's some confusion. I'd like to see us look at some gradation of the results in the drug study, but at the same time, I think a remission ought to remain what most of us think of and we shouldn't water that down.

DR. ATHREYA: But Bob, what duration were you thinking of, because that's one of the questions, the time element, two years or six weeks or six months or two months?

MR. LIPNICK: I like six months. I mean, I think it's something that we can get the numbers on. I think because of the natural course of disease, that if you go out to two years, you're going to be looking at natural course of disease a lot of times and not that.

I'd be interested in, Sandy, whether you have any comments just from your experience in the pediatric oncologic world for years regarding how we ought to maybe look at this.

DR. LEIKIN: I think the gentleman over there described what's been done in oncology. The only thing I could add is that certainly you have some parameters that you can use like a tumor or a bone marrow that you can measure, so you could include those in the secondary questions that you're asking.

DR. ATHREYA: Actually, there was some study in adults which I remember. St. Bartholomy Hospital in London, they had a consensus conference. I think they had similar to the oncology stuff. They did say, use partial, complete for the definition for both and then the remission. It was in Lancet a few years ago.

DR. SILVERMAN: Can I add something to the definition of remission, and that would be a functional outcome. If we really believe that what we're doing is altering, and we heard a very nice talk by Lori going over really well, just--and I think this maybe addresses Carol's point, inactivity versus remission.

To be in remission, you have to have a good quality of life or a functional ability, and I guess that's a better word than quality of life. But maybe it is. Maybe we need both of those and they should be in there and it should be unbelievably strict, because to make a claim of a remittive agent should be difficult, but not to say that a non-remittive agent isn't very beneficial.

DR. HEPBURN: You know, I'm not sure that's true, because even in oncology, suppose somebody has a leg amputated because they had an osteosarcoma. They can still be in remission and the quality of their life or their function has been affected. But that hasn't anything to do

with remission of the disease.

DR. SILVERMAN: But you'd expect improvement. I didn't say normal quality. One should build in parameters. If you have Pauci arthritis and you have joint damage and you're on an agent, presumably, it must be altering your function and you must be able to get improvement in your function, and that's all I'm saying. I didn't say it has to be normal. Actually, maybe quality of life isn't, but you'd expect an improvement, a functional improvement.

DR. RIDER: What if you have had very longstanding disease that's chronic and you can't attain any improvement in function?

DR. SILVERMAN: Then why are you on the agent if you don't have active disease?

DR. JOHNSON: For your other joints.

DR. SILVERMAN: But that should--if your tool is adequate, it should pick it up.

DR. JOHNSON: If we want our tool to include everybody in the population--we couldn't get to that state in the adult world. We had to make a cut and say, remission is going to only occur for those who do not have this kind of pre-defined structural damage already.

DR. SILVERMAN: And that's reasonable, or you use a tool like Caren Duffy has, where one could pick parts of

the tool out for that patient, the design or functional.

DR. JOHNSON: Yes, Dick?

DR. STEIN: Stein, FDA. On the one hand, I see people struggling with words like remission and how strict should remission be and this is a really difficult problem and it seems like it's a snag that's getting in your way.

On the other hand, I like the simplicity of this thought that pain-free and no joint swelling. It's a very simple thought and I like it. It seems to me we can get around both of these problems by just simply measuring in each patient how long was each patient pain-free with no swollen joints and simply use that measure as a measure of the quality of that patient's life, or not life, but the quality of that--the length of that--I'm saying it very badly.

The length of that period of time that they're pain-free and swelling-free is something that could characterize any drug and it doesn't have the problem with placebo. I think it would be a simple measure to deal with.

DR. ATHREYA: It may not be for the reason we heard from Dr. Giannini. There are patients who have complete control of disease. They keep on complaining of pain for a long time and vice-versa, so it may be difficult to emphasize pain as one criteria for remission. The

disease may go, have no pain, continue with pain, or the other way around.

DR. STRAND: Could we put up the ULAR definition one more time, just as a comparison?

DR. ATHREYA: But, see, one possibility is that we use maybe something like this, or start with something like this but reduce the time element. At least, that is a starting point and we can see how well it works.

DR. JOHNSON: If your definition has a time--

DR. WALLACE: --do it without drugs. Again, I'd like to stress, I think it's terribly important to have on drugs and off of drugs, because we have to realize that whatever we decide upon is not just for us here in the room. We use that to communicate and that goes to all the physicians we work with, the patients, with all the agencies, insurance companies, et cetera. We don't want less for our patients.

DR. JOHNSON: And I think you have to remember, too, that if you're going to jack it up from six months to two years, you're going to need to do two-year trials to support that assertion.

DR. ATHREYA: That's why I said--

DR. JOHNSON: No, two-year controlled trial, and I think we're going to have trouble arguing for one-year

controlled trials.

DR. ATHREYA: That's why I said we skip that but cut the timing down, is what I suggested.

DR. JOHNSON: Cut it down.

DR. MAGILAVY: But if a patient achieves remission while on drug, knowing that there is toxicity with those drugs, isn't it imperative that we see what they do--that we withdraw the drug and see what happens to the patient.

DR. JOHNSON: It depends on the toxicity, though.

DR. WALLACE: Sure, but that's--right. It depends, when are you going to stop methotrexate? If it took them two years of escalating the dose, you're not going to stop it in three months. Sure, but that's a different question than--at least, the first step is we've got to try to get patients into remission on drugs. Then we can go from there, but--

DR. MAGILAVY: I'm thinking of it from new drugs, where the toxicities are not well defined primarily.

DR. JOHNSON: Yes. We'll probably get into that more this afternoon. I think that's the angle he's coming from.

Dr. Mitchell?

DR. MITCHELL: Ray Mitchell, Georgetown. Let me give you maybe a patronizingly simple analogy. Most of what

I feel like I do every day is a firefighter and I try to put out the fire. One analogy is that my parents and my patients know that when the fire is out, you roll up the hoses and go home, and it may be hoses of anti-TNF or hoses of methotrexate, but they stop taking a pill.

The other thing is that we're measuring, and we'll hear more after lunch, measures of the fire, measures of the inflammatory process. I have a little less trouble, Kent, with sort of making the distinction between a Steinbacher anatomic deformity that results from disease and a disease that's still on fire, and I think our goal is that, hopefully, they'll stop maybe Steinbacher anatomic stage two, but the fire's out. So I don't think if you totally exclude the anatomically compromised, like the amputated leg, I think we miss something.

Now, we're imperfect, and we've heard Barbara Ansell's long-term follow-ups of synovitis in those 30-year JRA patients, but I think as best we can measure it, when the parameters of inflammatory fire are out, that's controlled, Carol, in all due respect. Until we stop the drug and it doesn't come back, I don't think we're in remission.

DR. STEVENS: Just building on what you were saying, with regard to remission, if you had already joint

damage or functional damage to the joint and then you--even if you affect a cure, the joint is damaged, so you will probably have joint pain. You may or may not have joint swelling. But you may have secondary joint damage with secondary osteoarthritis.

So I think the definitions for remission have to take into account that the remission is in the disease itself. Once the fire is put out, you still have burned properties, and so that we don't all get burned and charred, you have to realize that I think the definitions, we have no active synovitis, no actual articular manifestations, are much more appropriate for a remission than saying that the joint is having no pain or there's no functional limitation, the joint that has already been damaged and will more than likely go on to have further damage from probably secondary OA.

DR. JOHNSON: Carol?

DR. WALLACE: I've got a great idea. Let's do this. Let's--because I truthfully think we should decide on something. How about if we call it complete response? How about that, all right? And we'll have six months and no active synovitis, no extra-articular features, and the normal values of acute phase reactants are fine, or we can leave that off, whatever. How's that?

DR. ATHREYA: They have to be there, because it if was up, it has to be down. If it wasn't there, that's different.

DR. WALLACE: Sure. Okay. All right. Normal values if previously abnormal. How's that?

DR. WILSON: They will be normal if they were previously normal.

DR. WALLACE: Abnormal.

DR. WILSON: If they were previously normal, they should still be normal. If they were previously abnormal, they should be normal, ergo, they should be normal.

DR. WALLACE: All right. Normal.

DR. MILLER: So complete responses while you're on medication--

DR. WALLACE: Right.

DR. MILLER: --for a period of six months. If you're off medication for six months--

DR. WALLACE: I'm not going to have anything to do with that.

DR. MILLER: --then it's a remission. Then it's a remission.

DR. WALLACE: Then I think that patient is darn lucky.

[Laughter.]

DR. STRAND: That is the fourth thing?

DR. WALLACE: Right.

DR. STRAND: We're darn lucky.

DR. MILLER: But making the distinction between complete response and remission, whether you're on drug or off drug, without evidence of disease.

DR. WALLACE: If that's what people want, that's fine, but I want--

DR. MILLER: That sounds reasonable.

DR. JOHNSON: Any other questions or comments before we break?

DR. WALLACE: But what about morning stiffness? I am kind of a fan of not having morning stiffness, but I don't know if--

DR. JOHNSON: I think if there are significant manifestations of disease, they have to be included in this definition as having gone away.

DR. WALLACE: Jim? Do you want morning stiffness?

DR. ATHREYA: What is the question?

DR. WALLACE: Andersson doesn't include morning stiffness. Do you want that in the complete response or not?

DR. ATHREYA: If morning stiffness was there, then you're going to say it's active disease in some way.

DR. WALLACE: Okay. So less than 15 minutes?

DR. ATHREYA: So why bother?

DR. WALLACE: Going once. Going twice.

DR. STRAND: No active synovitis.

DR. ATHREYA: That is better, because some of these kids, as you know, even after the disease is gone, good remission, every time there is some weather change, they do complain about some stiffness.

DR. WALLACE: Okay. Now what do you think about--does everybody feel comfortable with no active synovitis, or do you think we should make it more specific and say no joint swelling? Again, how many kids are referred to you with no active synovitis, that's inactive synovitis, which obviously doesn't exist, but patients get sent to you with that, right?

DR. JOHNSON: That begs the question of whether or not this definition, even complete response, is going to apply to somebody with a degenerative knee.

DR. WALLACE: Well, no. No. No. What i'm referring to is people saying that, oh, it's just boggy synovia, implying that that's not active pannus in there.

DR. JOHNSON: Well, that's equivalent. That exact issue was brought up in the adult setting.

DR. WALLACE: So I would like to propose--why

don't we say, no active synovitis, in parentheses, no joint swelling, end of parentheses?

DR. JOHNSON: We're not going to come to a conclusion on this, but I think you're going to have to address pain. You're going to have to address function. You're probably going to have to address quality of life. I mean, it's--

DR. WALLACE: Why can't we come to a conclusion? Why not?

DR. JOHNSON: Well, I'm willing to give it a try.

DR. STRAND: Restate it.

DR. JOHNSON: Is there a general consensus that the definition should encompass everything that reflects disease? If that's the case, we can let you guys propose something, if you like. Or do you think there has--I mean, the way the adults did their definition of remission, which is what we just adopted without looking at it critically, was they went out and they interviewed normal people and they found that when you interview people with no disease, some of them still had one of the seven criteria, so they allow one out of seven.

Is that right, Vibeke, or one out of six, or something like that?

DR. STRAND: Yes.

DR. JOHNSON: So maybe kids--maybe normal kids get stiff when the weather changes, too. I don't know. That may bear on the definition.

DR. STEVENS: With regard to the stiffness, remember again, if you've already had the damaged joint, I think you want to consider the type of stiffness that osteoarthritis patients get, and they do get stiff after some inactivity. They get a short duration of stiffness, but they do get stiff and they do have changes with weather, changes with activity. Again, you have to keep in mind the remission or the complete suppression of disease activity is with respect to the ongoing disease, not what's left over.

DR. JOHNSON: What we need is feedback that you believe in principle this is worthy of trying to work on. We'll put together a proposal, or you can or we both will. That's what we're going to do, actually. We're going to try to write an addition and put it out on the docket, isn't that right?

DR. STRAND: It seems, Kent, that it's probably more reasonable that in adult RA--I hate to keep making the contrast, because I'm not trying to say that JRA is at all like adult RA--but I think we all said, 500 patients, you've seen one remission in trials, and we don't really believe that remission exists. But I think, depending on the subset

of JRA, there are remissions, some of which are not drug-induced. So it's very important, I think, to have that remission criteria.

DR. JOHNSON: Okay.

DR. RIDER: We'll take a break for lunch and reconvene at 12:45. Thank you.

DR. JOHNSON: It's 12:45 now. We'll reconvene at 1:45.

[Luncheon recess.]

A F T E R N O O N S E S S I O N

DR. MILLER: I'm Fred Miller from the Center for Biologics and I'll be trying to announce this afternoon's session here. This afternoon, we're going to address some issues related to clinical science development and review some of the ethical issues that were introduced before.

Our first speaker this afternoon is Dr. Christopher Wilson, who will talk about immune development in normal children. How should it impact on JRA development programs? Dr. Wilson?

CLINICAL SCIENCE DEVELOPMENT (I-III)

I. IMMUNE DEVELOPMENT IN NORMAL CHILDREN--HOW SHOULD IT IMPACT ON JRA DEVELOPMENT PROGRAMS?

DR. WILSON: Thank you. What I'd like to do is review some concepts related to the antigen immune response in normal humans and try to use that as a frame of reference for your discussions regarding the effects that immune manipulation might have in this context.

So what I'd like first to do is provide just a framework on what we ask our immune system to do and that provides some perspective on what can happen if it doesn't do it properly, one example, which, of course, is juvenile rheumatoid arthritis.

So what we really ask you to do, of course, is discriminate between self and foreign, and in vertebrates, we've developed a specific immune response that develops memory in an amplified recall response which we rely upon for vaccines and other strategies that preclude us getting infected over and over again with the same organism. Of course, then what it must do is exclude, eliminate, or kill the foreign invader.

By inference, then, deficits will result either in an increased frequency or severity of infections with pathogens, that is, organisms that can produce infection and disease in otherwise normal hosts, or the advent of infections with non-pathogenic or opportunistic organisms, and, of course, if improperly regulated, autoimmunity or potential malignancy.

In essence, then, what we can do is look at the kinds of infections that develop at different ages as a mirror of what is wrong with the immune response or what is immature about the immune response. On this cartoon, then, is illustrated some prototypical infections that are unduly severe at different ages, and as shown by the colored lines, where their peak incidence of unduly severe infection occurs, and then the decline thereafter.

What you can imagine, then, is that this is going

to be affected by about three things. Number one, the organism must have the opportunity to produce infection so that those that occur in utero are a subset of organisms that could produce disease but are those that can't cross the placental barrier. Those that occur postnatally, then, are going to be ones to which access occurs over time with age.

So if you look at the prenatal child, the child in utero, we see that we have a newly severe infection with a series of intracellular pathogens and there's a fairly precipitous decline in the severity of that disease shortly after birth. That is, although cytomegalovirus and toxo can produce infection up until birth and shortly after birth, we really see the most untoward effects in the first 20 weeks of gestation, and I'll come back and illustrate why that occurs in a moment.

In contrast, of course, herpes simplex virus usually is transmitted during parturition and there's a very sharp window of increased susceptibility, so that untoward disease begins essentially at the time of birth and ceases to be a problem after about two months of age, suggesting that there's some maturation in immune response going on during this window from late gestation until about two months that helps control infection with these intracellular

pathogens.

Subsequently, we see untoward disease occurring with organisms like MTB, which, although it produces infection and disease in individuals throughout life, is much more likely to produce disease in younger individuals, that is, 20 to 30 percent of infants will develop disease whereas only five percent of adults do when they become infected, and among those that become infected, it's much more likely to produce disseminated disease, such as milliar [ph.] or meningeal disease.

And then the last group to which we see an increased proclivity for severe infection are the capsulated bacterial pathogens which are major problems in the first one to two years of life, and by about four years cease to be more of a problem than they are in more mature individuals.

So if we take this, then, as the substrate upon which one can look at the immune function, we can project on that those functions that are inefficient until those periods of time when susceptibility ceases.

In utero, then, the reason for the incredible predisposition toward syndromes from CMV, toxo, and so forth is that, in fact, you have a numerical insufficiency up until about 20 weeks of gestation. That is, T and B cell

numbers are low. T and B cells first begin to appear at about 12 weeks and are up to pretty much adult norms by 20 weeks and the repertoire is also limited, that is, the range of receptors they express, also reaching nearly adult norms in the latter half of gestation.

So it would appear, at least, that one explanation for the particularly severe disease with CNV and so forth at this time is that there's simply not enough troops with the right recognition apparatus to fight the battle during that half of gestation.

In the latter half of gestation, susceptibility diminishes as the cells are present but doesn't completely reach adult normalcy. Furthermore, as I indicated, there's a window of risk for severe infection with herpes simplex virus, and I'll revisit data suggesting this reflects functional deficiency in T cell functions which mature beginning at about one to two months of age and are pretty much fully mature by one to two years of age.

Then the last function that matures and protects us from capsulated bacterial pathogens is the ability to synthesize antibody to polysaccharides, that is, the T independent antibody responses. So this is the basis which I'll try to go in more detail now.

Used as a prototype, infection with herpes simplex

virus, because in many ways, the defenses against it and the other intracellular pathogens that I mentioned are quite similar. So we really have two major components. That is, the innate or antigen non-specific immune defenses that are present immediately at the time of infection, and they include natural killer cell mediated cytotoxicity and ADCC activity, and antigen-specific T cell mediated immunity, which is absolutely required to contain active infection, without which infection will prove to be lethal.

Herpes simplex and CMV are somewhat unique in that they handicap CD8 recognition by blocking class one antigen presentation, so that's unique to those organisms, making it very dependent on CD4 effector function, which is certainly also true for organisms like microbacteria, toxoplasma, and so forth.

How do these T cells affect control of disease? They can do it in really three major ways. They produce mediators, particularly cytokines, such as interferon gamma and tumor necrosis factor, they mediate cytotoxicity, or they provide cognate help for antigen-presenting cell and B cell activation, at least in part through the CD4 ligan that in many respects functions like a cell-associated cytokine.

What I will do is focus my attention on the processes that occur in maturation of production of certain

cytokines, particularly interferon gamma, and of cognate help for antigen-presenting cells and T cells and won't have time to go into cytotoxicity, but suffice it to say that data that's available, which is most limited for cytotoxicity, is consistent with the notion that the same processes drive the maturation of these functions.

So let me begin by talking about interferon gamma, which our lab has had some interest in. Or let me talk first about NK cells. Then I'll come to interferon gamma.

So natural killer cells appear by six weeks of human gestation and reach normal numbers by mid-gestation. However, mature cytolytically active CD56 positive NK cells are diminished by about half in number even in mature neonates, reaching adult levels by about one year of age, which corresponds to the time when cytotoxic function appears also to be mature.

T cells, as I indicated, begin to appear at about ten to 12 weeks of gestation, as do B cells, and the total numbers and CD4/CD8 ratio relative to body mass are greater than the adult by mid-gestation. Of course, as the child grows, the thymus must continue to export a large number of cells and thalamic size relative to body mass, of course, is at its greatest during this period of life.

As I indicated, the repertoire of antigens that

can be seen by T cell receptors appears likely not to be limiting by term. That is, they're quite diverse and they have normal end-length additions. However, these cells are naive in their phenotype and function, which I'll elaborate on more later.

Typically, one surrogate marker that's used for the presence of naive T cells, that is, cells that have not yet encountered the antigen they're programmed to recognize, is the CD45RA antigen and almost all neonatal T cells are of this phenotype. These cells proliferate and make out to normally in response to some agonists, but their activation is more co-stimulus dependent and requires, it would appear, higher numbers or interaction to drive it. So this may limit the inductive phase of the response and their ability to proliferate and produce IL-2, the major T cell growth factors, intact should this occur.

However, even with full activation, their potential is reduced in the following areas: The ability to make interferon gamma IL-4 and certain other cytokines, their ability to provide B cell help, and their ability to mediate cytotoxicity. I will argue that the functions that are diminished here primarily reflect the naive status of these cells rather than an intrinsic inability of these cells to function.

Let me first show you some data on interferon gamma production from our laboratory. Several other groups have found the same thing was originally reported by Ivan Bryson's group. Focused on the left-hand panel, which is interferon gamma on the Y axis in a log scale, and on the right, on the X axis, is post-natal age. The lower set of data points are neonates, maturing out to six months of age. The upper set are adults studied in parallel. So you can see there's a five- to ten-fold diminution in production of this cytokine, despite the fact that proliferation of these cells and IL-2 production, not shown, is not different.

Now, what's the basis for this difference? Focus first on the upper half of this cartoon. T cells recognize antigen in general as short peptides bounded MHC molecules on antigen-presenting cells, shown here, which for CD4 T cells is Class II MHC on professional antigen-presenting cells, phyton dendritic cells, macrophages, and B lymphocytes.

When a naive T cell, that is, a T cell that's never seen the cognate antigen that it is programmed to recognize, first interacts with the antigen on that antigen-presenting cell, it executes a fairly limited repertoire of functions. Specifically, it makes IL-2 efficiently and proliferates efficiently. I will come back

to later the specific nature of the APC interactions with naive T cells, but it also appears to limit the antigen-specific inductive phased response in newborns.

But neonatal T cells, as I indicated, by definition are naive to the vast majority of exogenous antigens. Once they've encountered antigen for the first time and have undergone a round of proliferation, they mature in function and also increase in number, so that when these cells encounter antigen the next time, their repertoire of functions is increased.

They may make additional cytokines like interferon gamma, GM-CSF, TNF, and IL-4, and yet with more rounds of replication might differentiate into cells that in common jargon are referred to as TH1 and TH2 cells that I won't discuss in more detail today for lack of time. In any event these cytokines can feed back on the antigen-presenting cells, making them more efficient, which I'll come back to in a moment.

One might wonder why tautologically this is the case, and there is some logic to this compartmentalization between naive and memory cells. That is, in general, we start life with a precursor frequency of T cells that are going to respond to a given antigen of a half a million to a million cells. That's simply not enough antigen-specific T

cells to protect us from any infection. So the first job of a cell here is to reproduce itself so there are more troops to fight the battle. Once that's been achieved, of course, then you can go on fighting the battle by making additional infector cytokines. So the key here would appear to be going from this step to this step.

The hypothesis, then, to be addressed is, is it antigen naivete, that is, lack of exposure to foreign antigens, that is the basis for diminished interferon gamma production and diminished other effector functions in neonatal T cells. The prediction, then, would be that if antigenic naivete accounts for diminished interferon gamma production rather than intrinsic limitations in function, then acquisition of capacity for interferon gamma production should develop in parallel with antigen-specific memory T cells.

We can read out the presence of these antigen-specific memory T cells by the fact that if we add antigen to a culture and can detect a response, these cells will have expanded in number from their low initial precursor frequency. Otherwise, we wouldn't be able to measure them. So we will read out the presence of these cells by proliferation and then look for interferon gamma production in parallel.

An in vivo study was done by our group looking at neonates with herpes simplex virus infection. This is the same basic way of displaying the data that I showed you before. Focus first on the right-hand panel, which shows proliferation as thymine uptake on the Y axis and postnatal age on the X axis. We're comparing neonates in this set of data with adults with primary HSV infection.

What you can see is that there's a lag in the development of antigen-specific memory T cells of about three to six weeks in the newborn compared to the adult as measured by proliferation, which is paralleled exactly by interferon gamma production. That is, once we have detectable antigen-specific cells, they make interferon gamma as well as do adult T cells.

That's consistent with the following notion, that the basis for functional T cell deficiency in the newborn is likely antigenic naivete rather than intrinsic defect that cannot be overcome other than by increased age.

The data supporting it, I've just shown you, is that T cells from neonates with HSV infection acquire a competence during interferon gamma production in parallel with the development of antigen-specific T cells.

In vitro, we can prime these cells in a matter of days by exposure to an antigen surrogate, and those cells,

then, when restimulated, are as competent as adult T cells to make this lymphokine and others.

You can also show that there's a post-natal age-related acquisition of T cell competence. Perhaps the weakest argument, such that interferon gamma production is detectably increased by two months of age and close to adult norms by one to two years of age, corresponding in part with that age-related infection diathesis that I showed you earlier.

So there is additional data to support this notion that there's a delayed development of the antigen-specific immune response to neonates and infants that may handicap them, depending on the tempo with which the infection progresses. For an infection like HSV that progresses rapidly, the delayed tempo may be a major predisposing factor.

So in addition to the HSV data which I've shown you, there is a delay in onset of detectable delayed hypersensitivity, which is a measure of CD4 T cell function in response to mycobacterium tuberculosis and Candida infections, which may take several months in the infant, whereas it occurs rapidly in the more mature individual, usually by four weeks. In addition, there is a requirement for additional injections of certain antigens to induce a

robust T dependent antibody response in young infants as compared to more mature individuals.

So why is this? One possibility is that the system in the newborn is not only naive in terms of T cells but that the antigen-presenting cell compartment is not fully primed. Some data that Ross Petty has developed will support this notion, and I'll cite it more specifically later.

That is, as I indicated, when a T cell response to antigen on MHC, if it's a naive T cell, it's tougher to get the thing going. It requires a more robust stimulus, commonly also requiring what we refer to as costimulation by specific molecules in addition to MHC on the antigen-presenting cell. In fact, naive T cells and neonatal T cells are most dependent on being activated by cells we call dendritic cells, which are very rich in the expression of these costimulatory ligands, at least in mature hosts.

One pair of these is the B7-CD28 pair that amplifies the signal of the T cell, driving IL-2 production and proliferation with greater efficiency.

If we then move on to a memory cell, as I indicated before, we've expanded them in number and now their function is increased, so they make additional

cytokines which act on antigen-presenting cells to improve their function, and in addition, they express on their plasma membrane now with much greater abundance a protein called the CD40 ligand that binds a co-receptor on the antigen-presenting cell or B cell, more efficiently activating these cells, as shown here.

In the case of antigen-presenting cells, then, you enhance the ability of these cells, like dendritic cells, to activate naive T cells because they express more of the B7 molecule and others. Thus, the presence of memory T cells that antigen X may enhance the activation of naive T cells that antigen Y by priming the antigen-presenting cell system through a CD40 ligand or cytokines that enhance antigen-presenting cell function.

These interactions, specifically by CD40 ligand on the activated memory T cell to CD40 on the antigen-presenting cell, can also play an important role when the antigen-presenting cell is the B lymphocyte, which occurs in T dependent antibody responses. Driving B cell class and affinity switch in the development of memory B cells, and that's facilitating the antibody protection.

What I'd like to do now is illustrate some data suggesting that this may be a limiting factor in the development of the immune response in human newborns.

First, data on dendritic cell function in human neonates. The first data that I'll cite is data from Ross Petty's group in which they showed that the antigen-presenting function of neonatal blood dendritic cells is diminished, and this data is supported by studies by Mara Clerici and Jean Shur, as well. This occurs despite the fact that core blood is highly enriched in dendritic cell precursors relative to blood from adults which can be made to mature into functional cells in the presence of cytokines like GM-CSF and TNF and IL-4 or CD40 ligand, which are produced poorly by naive T cells, thus suggesting that that might be a limiting factor.

So what is the data that CD40 ligand expression is diminished on neonatal T cells, and here's some data from our group that's been supported by data from several other groups. Focus first on the upper two panels of data, which are the primary responsive T cells activated in vitro. On the X axis on this fax plot is CD40 ligand expression. In adult T cells, when they're activated, you get CD40 ligand expression, shown here, and, in fact, if we only looked at CD40 T cells, the vast majority are positive.

In contrast, if you look at neonatal T cells, you get very little expression. If, however, we prime these cells by stimulation with a surrogate antigen in vitro for a

few days and then restimulate them so that they're no longer naive cells being activated, these are adult cells and theses are neonatal cells, then the neonatal cells are at least as good at expressing CD40 ligand with priming as the adult cells, again, consistent with the notion that diminished production of this important mediator is due to the naive status of these cells rather than an intrinsic inability of them to perform this function.

So, then, what might be the role of CD40 ligand in the development of antigen-specific immunity? We know from the human genetic disease, the X-linked hyper IgM syndrome where there's a defect in this protein, that the absence of the CD40 ligand delays and reduces the amplification of the initial antigen-specific T cell response, diminishes macrophage activation, thereby predisposing to infections with organisms like pneumocystis and cryptosporidium and cryptococcus, and it ablates B cell immunoglobulin class, which, from IgM to IgGM and, for example, affinity maturation and memory.

I will illustrate some data suggesting this may be what's going on in part of the newborn and also provide some data indicating that CD40 ligand in abundance may normally be a limiting factor in the development of the antigens to the immune response and perhaps account for the lag that we

saw in the response developing to antigens in the newborns.

These data simply provide data from other studies--in this case, I'm citing work primarily from Granoff and colleagues--on the age-dependent acquisition of antibody responses in man. If we look at typical T-dependent antigens like diphtheria and tetanus toxoids, they're proteins, and one can show that a newborn can make an antibody response to these. In fact, even fetuses in the last half of gestation can respond to these, albeit somewhat less well. The optimal response when it's fully mature is by two to four months of age.

If we look, in contrast, at pure polysaccharides like H flu, as we all know, they are poorly immunogenic under two years of age. They reach an optimal response really after two years of age, closer to about four years of age, so they're the last to mature. We can take this category of antigen and make it look more like this by conjugating the two together, as has been done with the conjugate vaccines, thereby lowering the age at which an initial response occurs to one to two months, not quite as young as true protein antigens, and getting an optimal response between two and 15 months, depending on the nature of the conjugate we create.

I'm going to focus some attention on this because

this may provide some insight as to what it takes to get this response going efficiently, since some vaccines work well at two months of age and others don't reach full maturity until 15 months of age.

So these are some data, again from, in this case, Ward and colleagues, looking at antibody on the Y axis in response to three H flu conjugate vaccines. This one over here is an orderly practice vaccine. This is the Mura U Kennaut [ph.] vaccine and this is the Merck vaccine. The blue bars are the primary response, the red bars are the secondary response, and the open bars are the tertiary response.

What you can see is that the tertiary responses are identical between them. They're all equally good if you give them three times. In contrast, there's only one that gives you a robust response at two months of age with a single injection and that's the Merck vaccine. So what is it about this vaccine that makes--that kick-starts the immune response more efficiently, and will this tell us anything about what's limiting the response in the normal newborn?

One possibility would be that the B cell repertoire for function was limiting. This seems unlikely because, in fact, if you look at the antibody made against

these conjugate vaccines, it uses the same B regions as antibody made against pure polysaccharide. So although this is likely to be--function is likely to be a limiting factor when pure polysaccharide is give, it's not the repertoire that's limiting.

Then the question is, is it T cell inability to provide help for B cells, the limiting function, which we believe is the case, and then question then is, is the vaccine immunogenicity linked to its capacity to induce antigen-presenting cells to effectively activate naive T cells, thereby allowing the T cells to help the B cells.

So to address this, we turned to some murine models where one could look at this, where we have now on the left-hand axis is the Kennaut Mura U vaccine, and you can see it's a lousy immunogen in mice, with antibody on the Y axis by isotype here.

If we use the Merck vaccine, it's a pretty darn good immunogen. With two immunizations, we get a response that's quite high and we get a pretty good response with a single immunization. It's predominately IgG, so it's class switched, suggesting that what we see in the human, with the hierarchy of the Merck vaccine being stronger, is also true in the mouse.

So why does the mouse do better with the Merck

vaccine? Well, at least in part, we think this is due to the fact that the Merck vaccine induces good costimulatory interactions between the antigen-presenting cells and T cells. We're looking now immunohistochemically for the expression of these costimulatory ligands, in the blue bars in mice that got nothing, in the red bars in mice that got the Merck vaccine, and in the white bars in the mice that got the non-immunogenic Kennaut or U vaccine.

What you can see is there's a strong correlation between induction of these costimulatory ligands and interferon gamma and vaccine efficacy. Furthermore, if we administer agents that block these interactions, we can ratchet this response dramatically down, suggesting that they are playing a causal role in the more robust response.

So what I've suggested, then, is that CD40 ligand and the reciprocal costimulator interaction B7 and CD28 play an important role in acquisition of IgG class antibody production. What I'm also going to show you is that the reduction in CD40 ligand in abundance that we see with human neonatal T cells may, in fact, be sufficient to account for poor or less robust induction of the immune response.

To address this, we created some transgenic mice in which we could overexpress the CD40 ligand using the human IL-2 promoter so it's on and off very quickly, just

like the normal gene is, but that this would allow us to express slightly more CD40 ligand or have it come on earlier. And in reality, what we achieved in these mice was about a 30 to 40 percent increase in CD40 ligand abundance, so not very much, less than the difference between an adult T cell and a neonate T cell and the amount of CD40 ligand they express.

Nonetheless, this relatively minor increase in CD40 ligand expression was associated with a dramatic increase in antibody production, particularly IgG antibody production, as shown here. Focus your attention on the right-hand panel of data. This is a logarithmic scale of antibody titer in mice given in model T-dependent antigen, T and B KLH, and what we're looking at, then, in the red bars is control animals and in the blue bars are the transgenic animals that have 30 percent more CD40 ligand.

Since this is a logarithmic scale, what we see is there's about a five-fold increase in antibody very early and this persists, although to not as great an extent later, suggesting that a modest difference in CD40 ligand can radically affect the rate at which one develops this T-dependent antibody response.

So to return back to my cartoon before, what I've suggested to you, then, is that in utero, there's a paucity

of T and B cells that's corrected by mid-gestation, as is the repertoire that those cells can respond to, of antigens they can respond to. There's a window of time where there's a profound increase in susceptibility to agents like herpes simplex virus that only lasts through about two months of age.

What I will tell you also is that's about the time when we see the first incremental increase back towards normal adult values of things such as interferon gamma and CD40 ligand that are products of memory T cells. Nonetheless, we do not see a normal amplitude of the inductive phase of the immune response until about a year of age, by which time we cease to see an increased risk of infections with organisms like the M tuberculosis and we stop seeing trouble with organisms such as respiratory viruses more than we see in other individuals.

The last response to mature, as I indicated, is the production of T independent antibody to polysaccharides, not maturing until about four years of age, and this appears to reflect, and is yet inadequately characterized, intrinsic difference in B cell function.

In addition, the increased predisposition to these extracellular pathogens may be accounted for in part by modest diminutions in compliment and in neutreal [ph.]

function that mature within the first two to four years of life to be comparable to those of adults.

So by and large, what I can tell you is that antigen-specific immunity and most of innate immunity is not radically different than an adult by about two to four years of age. Furthermore, there is a diminution in the absolute output from the thymus relative to mass occurring sometime beyond this time, so that beyond about four years, I wouldn't anticipate much difference at all. Between two and four, very modest differences, and before about two years of age and particularly under two months of age, you may be encountering an immune system that's certainly less prime and not as functionally competent.

With that, I'll just close with a list of the people who did some of the work and move on to the next person.

GENERAL DISCUSSION

DR. MILLER: Thank you very much, Dr. Wilson.

I believe that we're going to have discussion of each speaker as we finish here in this particular session here. I might start while others are thinking of their questions or comments. You've addressed the early developmental periods here, but how about the period when hormones begin changing and you start moving into the period

of menarche and so forth, puberty?

DR. WILSON: Yes. The question is, what about puberty? Well, basically, the one thing you obviously see at the onset of puberty is that's when you see a big upswing in autoimmune disease, particularly in the female population. It's fair to say, also, that I don't think we fully understand why that's the other age where we see a slight blip in TB susceptibility, the basis for which is not really understood.

There's nothing that we can show is intrinsically different about how T cells respond. However, it has been shown in a variety of systems that the milieu of hormones may affect some of these functions. You're probably aware of data from groups like Ray Dean's that suggest, in fact, that estrogen biases one towards making things like TH1 cytokines, where as androgens do the inverse.

So it may be that there are effects going on at that time that modify the nature of the effector function, rather than are intrinsic to the T cell itself or the B cell itself.

DR. MILLER: Are there any other comments or questions?

DR. LOVELL: Are there known environmental or host factors that affect the normal maturation process,

particularly early on in neonates?

DR. WILSON: Yes. There are some. Part of it simply is the exposure, so that if you take an autobiotic animal, for example, you can show the lymphoid tissue is much less robust. The responses develop more slowly in some contexts.

So that in terms of placing a child in a day care center and so forth, you are going to get a much more robust development of responses to those specific antigens over time and it will develop more quickly, even though the kid is going to be sicker more often. It obviously places those kids at increased risk, as well.

So I think the major difference there is what you change the most is the exposure and the acquisition of specific infections. Without necessarily modifying the intrinsic development of the system, you've changed what you've imposed on the system.

DR. SILVERMAN: Is there an IL-2 transgenic that would obliterate the response? Will IL-2 overcome early on a system--

DR. WILSON: To my knowledge, we don't have any data on that. So the question Earl is asking, I'm sorry, for those who didn't hear it, is if you provide IL-2 in trans or increase the amount of IL-2 produced, will you

amplify the system?

Certainly, one would imagine that you might do that in a non-specific way, but to my knowledge, that has not bene proved.

DR. SILVERMAN: So one of the reasons, of course, we are having your particular session here is to try to address the issue of are there special considerations for juvenile rheumatic diseases versus adult diseases that relate to immune system development, and I guess my take-home message here is after age four, there probably isn't that much of a difference that would relate to specific, at least biological modifiers relating to the immune system. Is that correct?

DR. WILSON: Yes. I would largely agree with that. Obviously, that will depend a little bit on what the individual has encountered. I think the key thing that's happening during this time of life, other than this intrinsic apparent maturation of the B cells, is that you're acquiring a whole body of primed memory T cells and that most of the agents that one might entertain, CHLI4IG, anything that blocks the specific immune response, is going to have a much greater impact on naive T cells. It's much easier to block the activation in prime naive T cells than in memory cells.

That comment notwithstanding, most of the agents that one would use, other than perhaps CD4, which would deplete CD4 T cells, seem not in humans to induce tolerance very well, and tolerance, although it's easily achieved in young mice, for example, is much less easily demonstrated in humans, which are much more mature at the time of birth immunologically than a rodent. So to get the same sort of window of time where you'd be worried about tolerance induction, you've have to go back to the first half of gestation in humans.

Having said that, there's some very subtle evidence that if you take small, very small infants in the first few weeks of life, there may be some slightly greater tendency with certain types of antigens to attenuate the ultimate amplitude of the immune response.

Dan, you had a question.

DR. MAGILAVY: Yes. Are there age-dependent differences in repopulation of naive T cells?

DR. WILSON: Yes. The question is, is there an age-dependent difference in the rate at which one repopulates the naive compartment. Obviously, RA is a surrogate marker that's imperfect. We know that they do switch back some.

There's no question that, in fact, the naive T

cell output is highest relative to body mass in utero and right after birth, so that if one came in with an agent that specifically ablated T cells in the periphery and in the thymus, you certainly would likely have a numerically greater impact the younger the individual you treated with those sorts of agents.

I guess we don't know the answer to what would happen if you went in in the first few weeks, months of life with an agent like a depleting CD4 antibody. I would be concerned about it at that time in life. You can argue that it's at a time of life when you're maybe most susceptible to tolerizing cells. It's also a time when the factory's got its highest output, which might allow it to recover more quickly. Certainly, the output is higher at that time of life.

DR. MAGILAVY: But you don't envision there being a difference between the adolescent and the older child?

DR. WILSON: No. I don't think so. I think if you have an adolescent female, I would argue that you're going to have the same immune status as of an adult female, a hormonally reproductively active adult female. Then you're not going to see much difference other than until you go back to the preschool years.

DR. RIDER: How about in the years of one to three

years of age, where there's a big peak for JRA in incidence?

DR. WILSON: Yes. Well, one might argue--I don't know why that is. What that suggests is that you've got--you can develop a T cell-dependent antigen-driven response that's deleterious, and I think that's consistent with the fact that many functions have matured in that first year of life. There's a dramatic diminution in risk and improvement in response to a variety of antigens by year of life, so there's a whole lot going on in that first year. I'd be most concerned about that time. I'd be very concerned about the first two months, and I'd be progressively less concerned and not very concerned after about four years of age about it being different from a more mature host.

DR. SILVERMAN: Can I ask another question about tolerance? Would you predict that if you could come up with a tolerizing agent would it work more effectively early or do you think it'd actually be more detrimental, or no effect?

DR. WILSON: More detrimental or work better?

DR. SILVERMAN: Yes. Or no effect. You have your choice.

DR. WILSON: As I said, there are some very weak data with antigens administered within the first day or two

of life, with a couple of antigens. Pertussis is one that you may have a less robust response later on. There's some unpublished data in a specific population that is Alaskan Eskimos that suggests that you might with some conjugate vaccines be able--with one conjugate vaccine be able to induce this at birth and not at a later time in life. But certainly by two weeks, that window of opportunity seems to be lost, and it's very difficult with most antigens to get a tolerizing response in human newborns.

By the time you guys are going to be concerned about something that's not due to maternal transfer of autoimmunity, I think that would cease to be an issue in my mind, at least largely.

DR. MILLER: Thank you very much, Dr. Wilson.

We'll move on to our next speaker, Dr. Ildy Katona, who will give us a summary of JRA immunopathogenesis. How should it impact on JRA development programs? Ildy?

II. JRA IMMUNOPATHOGENESIS - HOW SHOULD IT IMPACT ON JRA DEVELOPMENT PROGRAMS?

DR. KATONA: Thank you, Fred.

When I was preparing this talk, I thought that I have to have a concept and there are just a lot of things that I have to pull together, and not only immunology of JRA

but since we're talking about biological agents which are mainly going to be developed first for adult RA, I thought that I need to bring a little bit of comparison as well as I would like to just in the general concept put into that what are the feasible things under current knowledge in children and what are the ones that we already know that are not going to be feasible.

Then we're going to talk about the immunology. We also need to know that to do synovial biopsy, to do ultrasentesis [ph.], all of the procedures are much more difficult in children than in adults, so I'm not going to have as many data for you in situ from the synovium as an adult rheumatologist who would be standing here. May I have the first overhead?

I got special permission from Dr. Strand to use a copy of a table from one of her articles which very nicely summarizes the two major ways the immune system could be altered by biologicals in the case of rheumatoid arthritis. One is if you go to the bottom of the page is the potential for antigen-specific techniques.

This is the place where I would like to pause just a few minutes and tell you about what happens in adult rheumatoid arthritis. The trimolecular complex that we already mentioned this morning, the T cell, the

antigen-presenting cell, along with the antigen is really the one which is very critical at the initiation of the immune response. In adults, we know that the T cells are TH1s. They have a clonal extension in most of the patients, a particular V beta type which is V beta 14. There is a very strong MHC association with HLA DR4 in adult RA. The only thing which is not know is the antigen.

Later on, they are going to be talking about pediatrics, and I think from the morning discussion, you already have a Larabeta case that it's not as easy and simple in children.

Once the T cells became stimulated through the T cell receptors as well as by the participation of the costimulatory molecules and SK apertosis [ph.], then they will release cytokines and active macrophages, fibroblast B cells. The result of this is going to be recruitment of the cells into the synovium, synovia proliferation, and then the secondary cells are going to start to release all the different agents which are going to basically result in the joint damage that we see on the MRI or on the x-ray.

So the non-antigen-specific techniques kind of group together all the different possibilities that these non-specific immune responses are going to be able to be altered, and what I'm going to try to convince you, that

while the antigen-specific part of the immune response is different in children, the non-antigen-specific techniques are very similar, just like Ed Giannini was telling in the morning, the final common pathway. The next one, please.

You also heard a lot of discussions this morning about how to subdivide the groups of JRA, and if you really want to be very specific, there are many, many groups based on generic association, but I took the liberty and took systemic onset JRA out from the group. If you look at the top of the slide, we're talking about mainly the systemic manifestation and then the severe joint disease is going to be also representing at the time that I'm going to talk about articular disease.

We heard this morning that disease activity in these children could be really severe. They have fever. They have the acute phase reactants. One of the therapies that we invariably are using is steroids, among many other things, and nothing is really so far has been shown to control this disease. Based on the combination of the disease activity as well as the steroid therapy, these children invariably have severe growth retardation. The next one, please.

Now, it you'll look at the peripheral blot, what are the different immune abnormalities which have been

detected, and I think for this particular disease, that's a good place to look at, since probably giving that a good mirror of that immune system. There are a lot of cytokines that you could either detect in the serum or if you take the cells, they will be produced in vitro. TNF-alpha is one of the major ones.

IL-1, and this is a very interesting story, because at the beginning, in studies, IL-1 in some studies were elevated. Some other studies was normal until they actually realized, and this was Ann Marie Pierre's original observation, that these children have an inhibitor in their urine which later on turned out to be IL-1 Ra. They also have IL-6, so they have a lot of these cytokines which can be made either different cell types.

What is behind all this? There are still the original event of T cell activation. There are a lot of IL-2 receptors floating around. If you look at the immunoglobulins, these patients have fully clonal immunoglobulin elevation in their blood. The next one, please.

Very interestingly, there is a tendency of these children to have a lot of problems with hepatotoxicity and, in general, drug toxicity, and I think a specific syndrome, which is the macrophage activation syndrome, and the hepato

mechanism of the macrophage activation syndrome might give us the clue that what is really going on.

If you take children who just have systemic onset JRA and you very carefully study them, you're going to detect very similar abnormalities in these children except in a lot lower scale than in children with macrophage activation syndrome. These children, and I'm right now just trying to focus on the ones who have an associated systemic onset JRA, will develop fever, hepato- and splenomegaly, depression of blood counts, elevation of their liver enzymes, and there will be signs of fibrinolysis with hypofibrinogenemia, as well as dedimer [ph.] elevation demonstrated in their blood.

This particular disease could be a lethal disease. Children have been published who died of the disease. It seems to be that the major cytokine which is responsible for this is TNF-alpha and that is both in vitro evidence for increased TNF-alpha production as well as some indirect evidence in vivo. For example, if you look at triglyceride levels in these patients, they are very high due to the inactivation of the liproprota [ph.] in live case.

It's speculated that TNF-alpha is probably secondary to an original T cell activation and even though we do not have direct data, but one of the therapeutic

agents which works for this particular complication is cyclosporin, so I think this is a model which might be very useful in studying TNF-alpha.

After the systemic part of the disease, I would like to concentrate on the articular disease in JRA. The next one, please.

We already discussed that, basically, the articular disease could be devastating in systemic onset or polyarticular JRA, and I know that this might be somewhat confusing to a few of you, but there are two groups which start out as polyarticular JRA. They are the rheumatoid factor positive ones and there are the ones that are the rheumatoid factor negative ones. There is also a subgroup of the Pauci which progresses to poly JRA. The next one, please.

If we look at the rheumatoid factor positive poly JRAs, this is a very adult-like disease. They could have erosions, x-ray changes, very similar to the adult, as well as they have the very same genetic association, and not only the DR but the shared epitope, which is between DR1, 4, and 6, which is characteristics of adult RA. The rheumatoid factor polyarticular JRA children have that, as well.

Systemic onset JRA, which is very often a progressive and destructive joint disease, has no particular

strong HLA association. Many different HLA types have been shown to be associated with it.

The rheumatoid factor negative polyarticular one, this really represents a spectrum of diseases, some of them mild, some of them severe, more like what you see in adult rheumatoid arthritis, and the ones which start out as a Pauci, they have a particular DR and a unique DP association. The next one, please.

If we are going to look at the different published articles about the immunology, arthritis, and the synovial abnormalities in these different types, it's pretty much going to be the same, what you're going to see. So from now on, for all these articular forms, and these are mainly concentrated in the joints, what I would like to point out.

The cellular infiltrate is a CD4 positive T cell. It's usually increased CD4/CD8 ratio and they are, unlike the newborn B cells, these are CD45 RA negative, RO positive, CD29 positive memory B cells, memory T cells, and if you look at them, they have HLA-DR which is expressed on them. Resting T cells do not express HLA-DR, IL-2 receptors and the OKT9 antigen. So basically, these are the activated T cells.

If someone looks at synovium very carefully, then dendritic cells could be very nicely demonstrated among the

T cells, and dendritic cells are extremely good antigen presenters with the HLA-DR. So, basically, we have the same set-up as adult RA, and similarly to adult RA, we do not know what is the antigen.

Role of the trimolecular complex, the MHC, the T cell receptor, and the antigen, with the MHC. I'm going to have the next overhead a little bit tell you about the MHC association in Pauciarticular JRA in which the strongest MHC association we have. The T cell receptor repertoire in children is different. It's not a clonal extension but a polyclonal extension. However, there have been certain families of T cell receptors which have been favored.

The antigen, there have been a lot of studies which have been looking at antigens, and so far, the candidates have been viruses such as rubella, bacteria like chlamydia urusinia, bacteria of several components, heat shock proteins [?], and so on, but still, at this point, we do not know what is the antigen which initiates, or whether it's one antigen or whether it's multiple antigens. We do not know or have any information.

Once the trimolecular complex activates the T cells, then lymphokines will be released. The lymphokines will activate macrophages and fibroblast and the particular cytokines, mainly IL-1, TNF-alpha, IO6, again, this is not

an exclusive list, which are pro-inflammatory, and along with the lymphokines released by the TH1 type, which mainly are IL-2 and interferon gamma, IL-2, similarly to adults, have been shown to be present in the children. Interferon gamma potentially could be--this is going to be the amplification arm of the immune system.

Just for one second, talking about the potential effect and the potential balance between the TH1 and the TH2 type of immune system, it has been shown very well in adult RA, and I think theoretically it could be working in JRA, as well. The products of the TH2 type of cells, IL-4 and IL-10, have end-type pro-inflammatory properties, so basically those could be helpful in these diseases. the next slide, please.

Adhesion molecules subsequently get upregulated in the endothelium of the small blood vessels. The blood vessels also express HLA1 molecules. Subsequently, the monocytes, macrophages release certain enzymes, the most common metaloproteinases. There is much less data about these in children than in adults. On the other hand, there is really no data at the current time on the contrary, so these are potential areas.

Other cells, we know a lot about B cells. We know that there is an increased number of B cells. There are

many plasma cells. There is an increased percentage of the CD5-positive B cells. There is a polyclonal extension of immunoglobulins in the periphery that are autoantibodies. Even though JRA does not have the classic rheumatoid factor, children with JRA have the hidden rheumatoid factor, which just means that all the binding sites are occupied. A lot of the children have the positive ANA.

At the current time, you really do not have a good grasp on what is the role of the antibodies, as well as the compliment immune complex in this disease.

I think more and more interest is starting to be generated in NK cells. NK cells more recently have been shown to introduce--influence isotypes which in the immunoglobulin responds as well as in mast cells, which are known to initiate and mainly amplify immune responses. So I think all of these areas are very important, both for drug development as well as, I think, continued research for our community. May I have the next one, please?

I just would like to spend a little time on the Pauci JRA as a disease which already everybody heard this morning that's clinically different, has no adult counterpart, and I'm talking about what some classifications will call early onset Pauci JRA. It has a strong association with uveitis, strong association with HLA, DR,

DQ, and DP, and you can see some of the particular ones which have been shown.

Not only that, but also, there is some very elegant data about outcome and HLA association. I think this is an extremely interesting research area, and when it is going to come to clinical trials, this might be an area that different groups could be stratified. The next one, please.

When I got my package to prepare for this talk, Dr. Rider asked me to answer a couple of questions, and from my personal clinician view as well as from the view as I reviewed the literature, I would like to give you the answers.

The first question was, when in the course of agent development should products or class of products be introduced in JRA patients? I think drugs of second-line therapy drugs which are already available, as well as IVIG alone or in certain combination--I think the combination, just like in progress in adults, definitely could be tried in children, and after hearing from Dr. Wilson, we have very few patients on the H2 and most of them, by the time they fail the other therapies, are going to be H4, so I think we might be doing well with that.

The others, particularly the non-antigen-specific

agents, after the initial trials in adults demonstrated efficacy, short- and potential long-term safety, and no profound immune suppression, I think that's probably important in the children. We really need to look at the specificity of the immune response. Something as general, like an anti-CB4 antibody, might be still too big of a risk what you would like to take on the children.

The children who have severe disease, if you look at the risk-benefit ratio, probably going to be the first one who we could justify conducting these trials.

It's also important that drugs are targeting the antigen MHC T cell receptor interaction which are developed for adults. RA should not be used in children except in the adult-like rheumatoid factor poly JRA group. The next one, please.

The next question was to identify some immunopathogenic factors in JRA that would seriously alter response to particular therapies and that should be used as stratification variables for clinical trials. I think systemic onset JRA, especially at the systemic onset phase--we struggled this morning just even to come up with the core set. It is definitely something that is important, as well as it's going to be important from the--to see that a drug reaction is going to be similar.

It might be different if I'm allowed a little bit to speculate that if you could affect the immune system and maybe dampen somewhat the T cell response, that might prevent the macrophage activations.

Rheumatoid factor polyarticular JRA is a very adult-like disease, very different than anything else we see. And then, at the third point, with the very different genetic variation, I think we have the possibility, lump together everyone or split the different generic groups. I think it's going to be a decision what the pediatric rheumatology is going to have to make.

I would be probably at the beginning in favor of lumping. Just like Giannini said, it's the final common pathway, and other than the initiating event, the path mechanism seems to be somewhat similar. The next one, please.

I have a couple of special issues, what I thought that I would like to bring up, especially to the industry. We talked a lot about Pauci JRA and how we are going to include into trials. I think this is a terrific disease, where there are only a few joints involved, that the direct gene or biological agent delivery to the synovium would be very feasible.

The other therapy which potentially would be

easily administered to the children, who are always afraid of any injections we want to give them, is oral tolerance. Now, I am well aware of all the problems with the collagen study and the no efficacy demonstrated. I'm talking about antigen which is going to be specific, but when we're developing therapies for children, I think the mode of administration is very important.

The second example that I would like to share with you, and this is from an article from Dr. Silverman's group, is the long-term IVIG therapy in systemic onset JRA. A lot of times--the next one, please--a lot of times, we spend some energy on discussions when how are we going to introduce a new agent, whether we introduce it early or late. This was really an excellent review that sometimes our predictions just are not going to be true.

They noted no difference whether it was used early or later in the disease. It had significant improvement in systemic features. However, the effect on the articular disease was unclear. Again, there is some divergence of the systemic features and the articular features. It was very difficult to decide whether it was satisfactory disease control or remission, just like our discussion this morning. And I think, also very importantly, in treating children, they observed the development of a second autoimmune

disease, mainly SLE.

So I think even though we believe that the immune system of the children is all mature, we might want to see complications not seen in adults. The next one, please.

Just summarizing, I would like to point out that the rationale for using biologic agents in the treatment of JRA, this is a chronic disease, just like adult onset RA, and it leads to short- and long-term disability even under the best circumstances using all the currently available drugs.

The immunopathogenesis of JRA has many similarities with adult RA that for some of the drugs can be tried. There are, however, differences, especially in the initiation phase involving the trimolecular complex.

Then there are some special issues in children, ranging from differences in pharmacokinetics to possible effect on growth, bone mineralization, general development, development of the hormonal system, and so on. Even though at the current time we think that the immune system is mature, I think we should be staying on guard and use therapies which are as specific as potentially could be on children. The next one, please.

If you remember this slide, what we originally started Dr. Strand's table, there were two parts of the

therapy, the antigen-specific and the non-antigen-specific. I think the antigen-specific one is going to be different in JRA. On the other hand, non-antigen-specific agents might benefit the children. Thank you.

DR. MILLER: Thank you very much, Ildy.

Given our time frame here, I guess we time maybe for just one question at this point and then we can ask other questions later on during the general discussion. Does anyone have any comments or questions at this point? Go ahead.

GENERAL DISCUSSION

DR. MAGILAVY: Ildy, on your list of non-specific immune modulators you had, almost all of them were--in fact, all of them were either neutralized, specific cytokines or specific inflammatory mediators or interfered with specific pathways. Do you see a role of agonists as opposed to antagonists and do you think that they would have a better safety profile than the antagonists would have?

DR. KATONA: I think this is pure speculation, but if you look at TGF beta and all its properties, I think that's one of the agents potentially could be used as an agonist. I think that pretty much goes very much the same as for adults, which is going to be giving less side effect profiles. That's very, very difficult, very difficult to

say.

I think if you get certain agonists which are--either antibodies which are humanized, I think--there are just a lot of other questions that I didn't even have time to get into, but if they are cytokines themselves, it's going to be the short-term/long-term side effects. If they are antibodies, it's going to be the validating inducing antibody response. So I think potentially the answer is yes. Specific, I do not know.

DR. RIDER: One more question. You said that you would advocate, you said, biologic agents in children with severe disease unresponsive to conventional therapies. Would you define severe disease and conventional therapies? Would you like them to fail methotrexate, or what would be your--

DR. KATONA: The way I would define that at the current time, if somebody failed methotrexate, probably six months with no response. That would be my definition.

DR. MILLER: Thank you.

Dr. Vibeke Strand is going to talk to us about anti-rheumatic agents under development for RA and future candidates for JRA next. Vibeke?

III. REVIEW OF ANTI-RHEUMATIC AGENTS UNDER DEVELOPMENT

DR. STRAND: Thank you, Fred. Thank you to the patient audience. I will try not to repeat too much of what we have already gone through.

What I thought I would do is start with an overview of what's been there, done that, and what's still around in adult RA clinical trials and how this might be applicable to JRA, with a bit of tongue in cheek.

Just briefly, just to use the terms that were coined at one of the OMERACTs, maybe it was the first OMERACT, and I think now we have decided not to use the terms, but when I was trying to make this slide, I was trying to figure out--I didn't want to use NSAIDs because it doesn't really fit, and so I started with symptom modifying anti-rheumatic drugs.

We are hearing quite a bit now about potential COX2 inhibitors, selective COX2 inhibitors, and whether they're promising to us or not, they seem to be very promising to their parent companies, so we're going to hear a lot more about them. They are in phase three trials. I think they're being looked at both in OA and RA.

Tenidap, we've heard quite a bit about recently, and I think we still haven't heard the last chapter no that product.

I think of all the five lypoxogenase inhibitors

that weren't so toxic as to not make it through clinical trials, only Zileuton more or less made it, but it's being used only in asthma.

In terms of new disease modifying drugs, as we call them, DMARDs or DCARTs or whatever, we know how that cyclosporin and methotrexate are synergistic, and because they are, you can use cyclosporin in much lower doses and therefore avoid much of its toxicity. That's very exciting. Of course, cyclosporin is about to go off-patent and become generic, and therefore we are going to hear a lot more about Neoral, which may or may not be a pharmacokinetically better product.

We have mycophenolate mofetil, which actually started at its parent company in both RA and transplantation, and I can tell you that because I wrote both of the IMDs. But somewhere along the way, the marketing folks said, you can make a lot more money in transplantation, even if there are only 20,000 patients in transplantation, regardless of the one to two million you may have in adult RA. So the trials were positive in RA, but as far as I know, they haven't been published. I understand that Roche has some kind of a program whereby if you would like to use it on a compassionate use basis in RA, they will provide you product.

Leflunomide, which had a phase two study published in the November Arthritis and Rheumatism, done in the former Yugoslavia, is finishing phase three trials, two in Europe and one in the U.S. and Canada, which will encompass a total of about 1,100 patients who will be treated for at least 12 months or longer. The comparison drug for many of these studies will be methotrexate, and so the discussion has been whether the leflunomide studies could rewrite the methotrexate label because they will have the combined safety experience to predominate anything that's been published so far on methotrexate.

But I think it's fair to say that leflunomide, mycophenolate mofetil is a purine synthesis inhibitor and a very interesting drug. It actually begins rapidly dividing cells for bone marrow and GI and lymphocytes. In the same idea, leflunomide is a pyrimidine synthesis inhibitor, but unlike brechenor [ph.] seems to have a better tolerability profile, again, targeting the rapidly dividing cells.

Finally, we come back to the love of my life, biologic products, and I want to move on to that. Not to belabor too many points here, but I think that biologic agents have been developed either to target specific elements of the immune response, either to remove activated cells or block their function, or maybe we just should call

them bad cells, or normalize elevated levels of cytokines, and so far, that's really as far as we've gotten.

Recently, we have several products that are attempting to target the trimolecular complex of MHC II-peptide and T cell receptor and thereby selectively abrogate an antigen-specific response without causing immune suppression. That's the marvelous ideal. I think we can aspire to it. I'm not sure that the products we have right now will successfully do that.

But if one looks at the different targets that we could aim either biologic agents at or, soon enough, traditionally manufactured products that are based on naturally occurring substances, we can look at the adhesion molecules. We can certainly look at the leukocyte. We can look at costimulation factors between T and B cells, and we can certainly talk about cytokines. In that sense, we certainly have products that are aimed at each one of these targets.

All four of these products are infamous for having been studied in rheumatoid arthritis and no longer being studied for a variety of different reasons. They were both chimeric and murine anti-CD4 monoclonal antibodies and the placebo controlled studies were confined to chimeric anti-CD4, where active and placebo were not shown to be

different. There was, in fact, one death in the combined studies due to infection and multiple cause.

But, in fact, with retreatment, the CD4 T cell counts were depleted to 27 to 42 percent of baseline levels even at one year. When the cells repopulated and the synovitis either didn't go away or recurred despite the low CD4 count, it was shown that these were the memory cells. They were CD45 RO positive. They were DR positive. They were IL-2 receptor positive. Clearly, the product had depleted the wrong CD4 cells, if that was, in fact, what it was meant to do.

The anti-CD5 immunoconjugate, interestingly enough, didn't really deplete. It brought T cell numbers down, but within 30 to 60 days, the numbers rebounded to within normal. The placebo responses in this particular trial, which was just published in July A&R, actually exceeded active at all time points. It was meant to be a one-year study with a primary outcome of 12 months, but, in fact, it was published at three, six, and nine months, showing that placebo was better than active.

The CAMPATH 1H monoclonal antibody, although never had placebo-controlled studies, showed very significant biologic effects. The lymphocyte counts were depleted. The CD4 counts stayed low much longer than the CD8 cells, for as

long as 20 to 36 months. And again, when synovitis either recurred or persisted despite these low CD4 counts, it was shown that the cells in the synovium were antigen-specific memory cells.

In fact, there's a fair amount of infectious complications with CAMPATH and at least two deaths that occurred immediately after treatment due to infectious complications.

Finally, the DAB-389 product, which was targeted to activated cells, T and B cells, with the IL-2 receptor, showed really no specific benefit in short-term trials and was not pursued in RA, but it is being pursued in psoriasis.

So we've moved on now, instead of trying to deplete T cells, to target activation antigens, and there are two "non-depleting" anti-CD4 monoclonal antibodies that are in clinical trials right now and we expect to hear more about them at the ACR meeting. One of them is a primatized IgG1 monoclonal antibody that's been shown in vitro to block CD4 interactions with GP120.

There are two companies that are actually pursuing humanized IgG4 anti-CD4 monoclonal antibodies. Acutely, these antibodies do not appear to cause T cell depletion. Chronically, it's less clear once you have a host immune response whether that will be true. I think the data has

not yet been published.

In terms of targeting B7-CD28 interactions, CTLA 4-Ig has been very positive in some murine models of lupus and other animal models of autoimmune disease and it's being looked at right now in psoriasis and lupus in RA. As to whether it will be a good idea or a bad idea, some argue that it could cause some type of a defect in the immune repertoire since it would be targeting basically the development of new B cell T-dependent responses. It's not yet clear.

Finally, there is an anti-gp39 monoclonal antibody, as well as a traditionally manufactured product that is designed to do the same thing, PIC23.

So, so far, we have not succeeded very well with dealing with cells or even coactivation antigens, and so we've moved on to cytokine therapy, and that's really occupied our interest in the last couple of years. There are a variety of ways of blocking cytokine effects, either through anti-cytokine monoclonal antibodies or through receptor antagonists, which are really models or manufactured models of naturally occurring products, or through soluble receptors, which are, in fact, truncated forms of a natural membrane receptor that are usually in some way associated with an immunoglobulin product so that

they can have a long half-life in the blood stream.

The monoclonal antibodies are much like the T cell dependent products that we looked at previously. Both the epitope and the monoclonal antibody really determine the binding efficiency, and according to whether they're partially humanized, fully human, as in produced by transgenic pigs, murine or chimeric in origin, we have some idea about whether they'll have a long half-life and relatively how rapidly they will induce an immune response.

The receptor antagonists generally are biologically inert and they compete with the cytokine for binding to the receptor. Therefore, they must bind a lot of receptor to have an effect. They've very selective, but therefore of low efficiency, and one needs to give large volumes of product.

The soluble receptor molecules are, to some extent, less necessary to have large doses but they must persist in the circulation, and that's why many of them have been linked to an IgG1 Fc molecule.

Of the products that we've looked at that target cytokines, although IL-1 RA had mild effects in an active controlled trial of 175 patients, there's a placebo randomized control trial in 400 patients that was just completed in Europe and I'm sure will be reported at the ACR

meeting.

Soluble IL-1 receptor really showed no response in both interarticular and subcutaneous administration studies.

We have two competing anti-TNF alpha monoclonal antibodies. One is chimeric and one is human. Both randomized control trials have shown that the active was better than placebo, and they've had very dramatic effects on the acute phase responses, both IL-6 and CRP levels, and I'll come back to that in a minute.

Then in terms of the soluble TNF receptors, there have been a variety of competing products. The type one, the p55, which has a theoretical advantage in that it has a longer on-off time in binding TNF so may actually stabilize better, the data has not been reported with this product, although there was at least one very successful study in Europe in RA patients.

The type two, or p75 receptor, Immunex has just completed a study in 180 patients where they showed that the active was better than placebo, and I expect we'll hear more about that at the ACR meeting. As well, AmGen has just started a study with a type two receptor binding protein.

Other products that will be coming down the line are a TNF alpha protease inhibitor that's also being developed by Immunex and an IL-1 converting enzyme inhibitor

that's under development by Vertex. So I think that we'll see quite a few more of these types of products, and the idea, of course, is to get at the specific cytokine which is felt to be pro-inflammatory without causing immunoregulatory difficulties.

There, I bring up these interesting findings that have occurred with the anti-TNF monoclonal antibody studies. The chimeric IgG1 has been studied in 73 patients in a placebo controlled trial and the humanized IgG4 in 36 patients in a placebo controlled trial. Both showed rapid marked decreased in serum IL-1--IL-6 levels and CRP levels, excuse me, not IL-1, although one expects that that would probably have gone down, too.

Interestingly, when one treats RA patients with chronic disease with an anti-TNF product, their in vitro T cell proliferative responses to mitogens and recall antigens actually increase, indicating that TNF has some role in that depression. There has been some work to show, in fact, that TNF has some role in the cachexia that's seen in patients with active RA that may, in fact, be ameliorated by treatment with methotrexate, and Rubinoff's group has just published another article on this observation in the July A&R.

But what's very interesting is with the chimeric

IgG1 monoclonal antibody. In the combined experience of about 100 patients, approximately six had developed anti-double stranded DNA antibodies, having had no predisposition to this before and having not had evidence of clinical lupus or lupus or RA or what we call rupus prior to treatment, and at least one developed anti-cardiolipin antibodies.

Sure enough, with the humanized antibody, two patients became ANA positive. One of them developed anti-double stranded DNA antibodies, and five became anti-cardiolipin positive.

The etiology for this is certainly not clear to us, but there may really be some immunoregulatory effect of TNF and not just as a pro-inflammatory cytokine, because we know in the NZVW mouse, when Jakob and group at Stanford studied high-dose TNF, it protected against development of disease, but when Brennan and group used low doses of TNF, they actually worsened disease in the mice.

The other interesting point here is that both of these anti-TNF monoclonal antibodies have now been reported to have very positive data in Crohn's disease, with a much more rapid onset of effect and a prolonged benefit. In general, these two chimeric and humanized antibodies have been beneficial at doses of ten milligrams, which is a huge

dose, if you think about it, not so effective at one milligram, and clearly the ten was better than placebo.

But the benefit tended to be short-lived in RA, on the level of about one to two, maybe three months, but then again, Bonnie can correct me because she knows the data much better. The interesting point with the Crohn's is that both of these antibodies after a single dose had been reported to have benefit for as long as six to 12 months in Crohn's disease, and why that effect should be so much longer lived is of interest. I think we'll learn more about the different diseases.

In terms of adhesion molecules, we've heard a lot about different kinds of ways that they could be inhibited. Theoretically, one would argue that to do that effectively, one would increase the incidence of infections. So far, really, only one product has been studied in RA and it's the murine IgG2a monoclonal antibody to ICAM-1, and those studies have been discontinued. The company is humanizing the product, but I think they believe that they will take this product to approval in transplantation and actually in graft rejection. To all effective interests, they're not interested in pursuing it in RA.

A variety of companies developed all sorts of ways to inhibit selections or integrins or block transcription or

translation, but so far, we really have heard very little about these types of therapies in RA.

The vaccine technologies, which all sound very exciting, except that it's kind of hard to understand how we can do vaccines if we don't really know what the putative antigen is. I'm not sure we really know what the T cell receptor is, either. But ostensibly, there would be a very nice way of affecting the disease if we could intervene somewhere in this recognition process here.

This is an old, old slide, from a time when I worked for a company that was actually pursuing this type of therapy in multiple sclerosis with some interesting results that were certainly positive. I think the nice thing to be said was that at least the data from that study and subsequent studies have shown that this really has very few side effects, if any, and it hasn't really created a "hole in the repertoire", and so the patients can tolerate this very well and still maintain their immune surveillance and their memory responses to recall antigens.

In terms of MHC blockade, there is now a company looking at an HLA DR4/1 peptide vaccine. They finished a phase one trial, which was really only single administration in DR4 heterozygous adult RA patients, but interestingly enough, about 25 percent of the patients developed an

antibody response to the vaccine, which would say that it had some type of a biologic effect. As to whether that will, in fact, correlate with a clinical response is still very much under speculation.

In terms of Tcr peptides, Immune Response has just finished a series of phase one trials, each with the V-beta 14, V-beta 17, and one with V-beta 3, and they just completed a three-peptide cocktail of V-beta 3, 14, and 17, and I hope we'll be hearing about that in November or October at the ACR meeting, as well.

In fact, these studies have been well tolerated, although they have used incomplete Freud's adjuvant to try and boost the immune response to this vaccine. I think most of us are skeptical that in outbred non-animal population, by the time we see clinical disease, the T cell beta receptor usage would be sufficiently restricted as to be benefitted by this type of therapy, but they are also pursuing this intervention in psoriasis and others are pursuing this intervention, again, in multiple sclerosis.

And finally, oral tolerance, which is perhaps the best tolerated of all the new therapies. It's interesting, the chicken collagen recent trial in 273 patients showed equivocal results in that they had to use an intent to treat analysis of any time versus baseline placebo versus active

and showed that the lowest dose had the most effect, which was interesting.

Alternatively, in 90 patients in Germany, bovine collagen, which is supposed to have more of a hemology to human, showed some very interesting responses in the patients, with several of them being able to stay off treatment for quite some time.

I think it would be interesting to study these therapies further because they're so well tolerated, but I don't think any of them right now are ones that we should be taking to the bank and investing in.

Gene therapy makes a lot more sense if we can look at a disease that is Pauciarticular, or we can look at OA, where there's one severe joint or several severe joints. There are a lot of candidate genes whose products are secreted, and we can get them into a synovial lining fairly well, fairly quickly after just an intra-articular injection. The problem really is, can we get the transduction to occur and can we have the transient or even the persistent expression of the gene product for a long enough time to down-modulate the inflammation.

I think what is interesting is that at the time now of PIP joint arthroplasty in patients with OA at the University of Pittsburgh, they are now a week before taking

synovial cells out and transducing them with the IL-1 RA gene, and then at the time of arthroplasty, they then remove the cells and see whether they are expressing or not and replace the joint. This protocol is not only underway, but I think it was two weeks ago that they announced that the first patient had been treated.

We have seen, I think at previous meetings, the interesting data with the rabbits, where their knees would be blue as long as there was a gene product being expressed, and I guess Chris Evans has promised his patients that there won't be any color associated with this one. But they're getting a new joint a week later, anyway. It should be a very interesting treatment ultimately for something like osteoarthritis or for Pauciarticular JRA.

I always put this in to remind you that we're not doing very well with our therapies, but we've thought about some very amazing aggressive treatments. They've been reported on an anecdotal basis, one of them being T cell vaccination. There have been three reports, in general, not very profound or beneficial effects, but people have tried it. I think the issue is, how do you pick the T cells and what should they be responsive to and then how do you inactive them before you thereby vaccinate the patient with those T cells?

Interestingly, there was recently a report of immunizing postpartum women with T cells from their spouses. In the seven patients who got T cells from their spouses, seven of them, or 46 percent, had improved disease activity, whereas the four who didn't get spousal T cells, and we're not sure why, only four of them got better.

Finally, there's a lot of interest in bone marrow transplantation, both autologous and allogeneic, and I think a lot of that has to do with--there's been at least eight cases in RA of either gold or D-penicillamine induced aplasia, where the patients have had allogenic transplantations. Although three of these patients have died, of the remaining five, four of them are in remission and one of them has had some improvement in disease.

The question now is whether we really could now get to the ultimate stem cell and look actually at autologous bone marrow transplantation as a way to ablate the active lymphocytes and completely reconstitute the immune system and reeducate the T and B cells, and I think with the new growth factors and the fact that people have ways now of getting to the hematopoietic stem cells, this is a promising intervention.

It would be possible to oblate with less severe toxicity because one really needs to get at the dividing

lymphocytes, and one could keep the red cells and the platelets to some extent in an autologous setting. One could certainly support people with growth factors. It's possible that, over time, if they could survive that difficult time when they are susceptible to infection, autologous transplantation may really be beneficial, and beneficial in ways that we had not seen before because we had no way of actually depleting the bone marrow of even the progenitor cells before.

Allogeneic transplantation certainly has been considered, and there are a couple of protocols that are wandering around looking for IRB approval in both severe systemic sclerosis and in lupus. I think that they certainly deserve consideration. One is a little concerned, though, that the mortality for allogeneic transplants is somewhere between 15 and 35 percent, due both to graph versus host disease and just the overall organ toxicity of the myeloablative preparation, whereas autologous transplantation really carries a three to five percent mortality. So it's quite different.

There is an international consortium now to look at bone marrow transplantation in severe autoimmune diseases, and at least the ULAR group is pushing right now a study of autologous transplantation with selected stem

cells.

So have we gotten somewhere where we can actually offer more benefit than toxicity? The answer is, I think we have, but we have to consider what the toxicities are. Although my slides say biologics because I decided not to make new slides, some of these products, as you can see as we move through here, will include some of the traditional drugs that we're used to.

We talked about infection. Clearly, that occurred with CAMPATH with a very profound depletion of all lymphocytes and CD4s for even longer than CD8s. We've heard about it with anti-CD4, although it's largely hypothetical. There's really only been one death in a patient receiving multiple treatments.

There were serious infections in this single blind treatment IL-1 RA of 175 patients, but without a placebo, it's hard to know whether that's really the disease population or the product. There's no question that there's been a higher incidence of infections and at least one case of sepsis in the trials with the anti-TNF monoclonal antibodies.

My answer is, I don't know. We have some feeling that adult RA population is more immunosuppressed. Is this really the true incidence of infection in the population or

is this due to the products that we have treated them with?

I think the same thing is true for malignancy and it's really less clear. We know that OKT3 is a mitogenic antibody and we know that in transplantation it's associated with development in non-Hodgkin's leukemias, lymphomas, particularly patients who have got very severe immunosuppression.

There are at least 15 cases of non-Hodgkin's and Hodgkin's lymphoma reported in patients receiving methotrexate, although by and large, many of them were reported to recede as soon as methotrexate is stopped. We don't know how many are reported. Lederle, now called Immunex, says that they only have eight case in their registry.

There are so far two NHL patients reported in the combined patient population of 140 patients who have received CAMPATH 1H, and, in fact, Glaxo-Wellcome is required to keep a registry on the CAMPATH 1 patients to find out whether this number will be increasing.

There are, so far, two NHLs and one Hodgkin's lymphoma in patients who have had the anti-TNF monoclonal antibodies, and again, I don't think we know what the underlying incidence in RA or even lupus is associated with treatment. We have shown that there is an increased

incidence in RA patients receiving cytoxan, but at the same time, I'm not sure that we can be that clear that that's true, say, with the lupus patients, and it's unclear how much of this, again, is the underlying disease.

Finally, of great interest are the autoimmune manifestations that have occurred with a variety of biologic agents, both in RA and in other diseases. Endocrinopathies have been very common in patients receiving IL-2 and in various interferons, particularly gamma and, to some degree, alpha.

G-CSF, which is considered to be much more benign than GM-CSF, since it's not supposed to activate those macrophages, has been associated with endocrinopathies, monoclonal gammopathies, and leukocytoclastic vasculitis, and, in fact, in the combined experience with G-CSF, more patients had difficulty with leukocytoclastic vasculitis because they did not have cancer but instead had a benign cause for neutropenia and were given G-CSF that's prophylaxis against infection. When their neutropenia would start to respond and their counts would get above 800, they would tend to have these leukocytoclastic vasculitis manifestations recur. So clearly, there is something to do with the agent as well as the underlying disease.

We know that CAMPATH 1H has been associated with

at least one case of hemolytic uremic syndrome and one case of TTP or ITP and another case of vasculitis, and I mentioned to you already the autoantibody picture in the anti-TNF treated patients.

So what should we do about JRA, based on what we know from adult RA? I think it's a nice idea, we could have an antigen-specific therapy. I think where we would want to look for it presumably would be either in the polyarticular rheumatoid factor positive patients who appear to be a lot like adult RA patients with the DR4 beta 0401, et cetera, heterozygotes and homozygotes, or possibly to look at the shared epitope of DR5, DR8, DR6 in the Pauciarticular JRAs.

But I think it's hard to say that we really are going to be able to find the putative antigen or really even recognize MHC associations and TCR usage in JRA any better than we are in the adult population, since we are not lab animals who have been very well inbred.

So despite a very benign approach, I think it may not be an approach that has a lot of promise unless we can do it prophylactically. Maybe we have to do it in relatives of first generation patients, et cetera.

Monoclonal antibodies have been around for a long time. We have been through the murine to the chimeric to the humanized. We now have transgenic pigs, as I mentioned,

who can make fully human monoclonal antibodies.

On that basis, I think we already have some knowledge clinically that immunogenicity has not been nearly the problem we thought it would be. The concerns, particularly with the humanized and the fully human monoclonal antibodies, are probably largely theoretical, although an immune response could limit chronic readministration of the product. Most of the adverse events have occurred not due to immunogenicity, and if they have occurred because of immunogenicity or in the context of an immune response, they've not been associated with either anaphylaxis or immune complex formation.

So, in fact, we think this is a theoretical limitation for future chronic treatment of agents that are immunogenic, but it may not be a real concern.

In terms of potential toxicities and infections and lymphoproliferative disorders, we understand that children, from a very elegant talk prior to this one, that after about four years of age, we have a fairly normal immune system. In fact, lymphocyte numbers and proliferation are very active in kids under the age of seven. Certainly, there are age-related differences in CD4 T cell regeneration. We have seen that from chronic chemotherapy to kids receiving it for cancers and lymphomas

and so on. The younger they are, the sooner their CD4 T cell counts bounce back, the sooner you can see that the thymus actually is regenerating its function and they're reeducating T cells and the less opportunistic infections they have.

In fact, in general, in kids who have received recurrent chemotherapy, a CD4 count of 100 or above has usually not been associated with the development of opportunistic infections, despite our experience with the magic number of 200 in adult patients with AIDS.

Interestingly, patients receiving transplantation have been relatively resistant to OKT3 and ATG therapy and, in fact, tend to need higher doses of both to deplete their T cells to respond to the transplant.

Finally, I think what's important in looking at kids, as it is in adults, but it's much less common, is the seronegative host who is going to receive a seropositive transplant for EBV, because clearly there's been a significant danger there and that is something that we need to continue to screen for.

In terms of organ-specific manifestations, there are differences. In methotrexate, the kids seem to be--the effects seem not to be different but the incidence seems to be far different. Hepatic is less. Is that because our

kids in general don't drink? Is it also because they have a more rapid metabolism? Hematologic may be more prominent. Pulmonary is rare in both situations. The incidence of lymphoproliferative disorders, I frankly don't know and I don't think we can answer that.

In terms of cyclosporin or neoral, obviously, nephrotoxicity is very important because in order to have normal growth, you need to have normal renal function, and I think there are other concerns with cyclosporin or with neoral, but perhaps the use of it in combination and in low dose with methotrexate will be safer.

We have to worry about the potential impact on bone mineral density. There's a lot of studies about high-dose methotrexate in kids treated for cancer and what happens to their bone mineral density, and there's at least a theoretical concern about the combination of methotrexate and prednisone in kids with JRA.

We heard some very interesting data, which so far can't be resolved, about the potential impact on bone marrow density in the tenadapt studies. So I think we're going to have to sort that out really for every product that we look at.

The questions about the autoimmune manifestations are largely unanswered and will be until we study these

agents clinically.

So basically, the recommendations that I would have for biologic therapies, as I would have for traditional therapies, is do we look at them in RA and JRA, is that we need to have safety established so we can look at patients who have early more modifiable disease. We've certainly got to continue follow-up beyond the protocol duration and even beyond the time that the medication or the biologic agent is administered. I think it's very important that we look at RCTs.

We can utilize placebo controls to learn a lot more and we can let them exit early from the protocol for defined lack of efficacy, and that can occur for any of the treatment arms. But I think it's important to have the type of control.

Something that we've overlooked a lot in our enthusiasm for looking at safety and efficacy simultaneously with biologic agents is we tend to overlook the detailed dosing and dose scheduling work that we really need to do.

Utilize the same outcome measurements? Well, we've talked about this a lot in adult RA and we talked a lot about it this morning in JRA. I think, clearly, we do have a core set of measures that we should use, and we can add others to it, but by having this core set, by being able

to stratify, presumably, then, we could, in fact, enroll a larger population of JRA, regardless of what the onset of their disease process looked like and we could live with however their disease developed, whether it became polyarticular or stayed systemic.

I think measures of immune function and biologic effect are tremendously important even with the "immunosuppressive" or "anti-proliferative" agents, and I think we really have to look at these combination therapies because we learned a lot from that methotrexate failure study where patients got low-dose cyclosporin or a placebo, and clearly, the combination was better.

So I'm going to gloss over the single answer and just say that promising new agents for the treatment of RA should be studied in JRA and many of them would be applicable. Perhaps the antigen-specific ones are not, but it's unclear that oral collagen or some of these other products shouldn't be looked at.

Once there has been tolerability demonstrated, I would argue that we should do parallel clinical trials in JRA, if they seem appropriate to the agent, because, in fact, it would benefit the sponsor to get an orphan indication for parallel development, and certainly I think whatever we learn in JRA helps us learn more in RA and

vice-versa. They're not the same diseases, by any means.

In fact, we treat HLA B-27 positive spondylorathropades and psoriatic arthritis and the arthritis associated with inflammatory bowel disease with the same drug we treat adult RA with, with the same drug that you're treating JRA with. And, in fact, it is really the only drug right now we have that works.

There are some other anti-proliferative immunosuppressive kinds of products in the pipeline that may be as promising, and beyond that, some of these biologic agents may be worth looking at simultaneously in both populations. Thank you.

DR. MILLER: Thank you very much, Vibeke.

I think we'll have time for one comment or question and one answer. How's that? Are there no comments?

GENERAL DISCUSSION

DR. WALLACE: I'll say something. Even in Seattle, where we're very enthusiastic about aggressive treatment, we actually did consider bone marrow transplantation but were unenthusiastic about it for several reasons. One is there's a report of, I think probably two adults who did, indeed, have their rheumatoid arthritis go into remission, but--or great clinical response,

sorry--complete response--

DR. STRAND: Fabulous clinical response.

DR. WALLACE: --but it recurred.

The second thing is that I think just about all of my patients would have a complete response to being irradiated and getting a lot of medications.

And then the third thing is, that actually came from Bardenepaum [ph.], was that if you get a really good match, they're going to have the same genetic disposition and probably get their disease back.

DR. STRAND: I agree that it's all controversial, no question, but the HIV patient who got the baboon bone marrow, I guess it didn't take. What a surprise. But he seemed to have gotten largely improved from his myeloablative therapy for a period of time.

I think in terms of the allogeneic transplants, there's probably promise because we've got new preparation regimens that we could use, but they haven't been used previously and people are reticent to try them now. From that point of view, I think it's not appropriate to do it because the organ-specific toxicity of these myeloablative regimens is really pretty terrible. The radiation in and of itself is pretty awful.

But if one could think about taking some of the

new combination therapies, like a purine synthesis inhibitor, you could probably get it. You're rapidly dividing cells and do them in without having to do in your lungs at the same time, but we haven't done it yet.

We know there's a genetic predisposition, but there's still an environmental exposure that accounts for half of it. Now, if you've actually been able to remove your lymphocytes to a great extent, will your thymus reeducate everything as if it saw it all the first time? I think that's a question, and I think it's controversial and the reason that the ULAR group chose to push autologous first was simply because of the significant safety concerns.

DR. MILLER: Are there any more questions?

DR. GIANNINI: Vibeke, regarding T cell receptor vaccines, there's no data in JRA. There are a couple of patients whose T cell receptor repertoire has been characterized on serial samples. I think the data in adult RA are clearer in that if you do serial typing of the T cell receptors in the joint, they vary through time. There's not one that's overly expressed all the way through. Isn't that your impression?

DR. STRAND: Absolutely. That's totally correct. In fact, I think it has a lot to do with how you actually grow up your synovial cells to see what the TCRV beta, the

expression could be, and if they've been exposed to IL-2, then you get a whole lot more of free 14s and 17s.

DR. GIANNINI: So is the rationale for giving a cocktail that there's polychromal expansion at one point in time? I'm trying to figure out the science behind that.

DR. STRAND: I guess the science may be that at some point, it was oligoclonal or one clone, and maybe if you can get it soon enough, you can do something with two or three--

DR. GIANNINI: With the--that aren't expanded yet.

DR. STRAND: That haven't gone the way of setting off a whole lot more immunoregulatory circuits. But I think that the data in humans is really not very good for that, since many competing labs have shown very different results, and so far, I don't think we've seen any clinical results that would argue that intervention has benefit.

At least one thing we've been able to show far from the studies, and that is that we haven't created a hole in the immune repertoire, but we haven't cured the disease, either.

DR. GIANNINI: Right. Also, Chris Evans' work, I think, is in RA. You said OA. Isn't it in RA?

DR. STRAND: No. I think these are OA patients, but I'm not positive. It may be both.

DR. GIANNINI: Does anybody know?

DR. JOHNSON: I think it's RA.

DR. STRAND: Is it RA?

DR. JOHNSON: I think it is RA, yes.

DR. STRAND: Okay.

DR. RIDER: Just a general question. I was just wondering if people on the panel here feel comfortable with introducing biologic agents and powerful new DMARDs and other such agents into our JRA patients. At what point in agent development would you feel comfortable? At what point in disease severity would you feel comfortable?

DR. STRAND: I guess I want to just defend myself for one second. I'm not suggesting we put it in all patients immediately, but you do as we've done in RA adults and you start with the patients who failed methotrexate or failed what's available and move down from there once you see tolerability.

But I think there are a lot of products that we probably have a profile coming down the road that's at least as good as methotrexate and deserve a good look.

DR. HEPBURN: I'd like to speak to that, as well. I hope that we have future products that are going to be safer and we shouldn't hold back on them if it's appropriate to go forward.

DR. RIDER: Does anybody else have any comments on that?

DR. GIANNINI: What Bonnie--in our FTA draft guidelines, Bonnie, you wrote that part, and I think that's what was stated in there and I think that's exactly correct.

DR. MILLER: Why don't we move on to the last presentation in this session before our break, which is from Dr. Sanford Leikin revisiting ethical considerations in agent development in JRA at this time. Sanford?

ETHICAL CONSIDERATIONS IN

AGENT DEVELOPMENT IN JRA

DR. LEIKIN: I'd like to first talk about the ethical requirements of introducing new agents for JRA and those requirements are based on the principle of beneficence, which requires that we maximize benefit and we prevent or reduce harm.

The ethical requirements are as follows. Any drug research to be conducted on children must be scientifically sound and significant. The risks should be maximized to the greatest degree possible [sic].

Whenever possible, research that involves risk should be conducted first on animals and adults in order to ascertain the degree of risk and the likelihood of generating useful knowledge. In general, children should

not be subject to an agent or a combination of agents that has not undergone some safety testing in adults.

When research involving risk is designed to study disorders that have no parallel in animals or adults, studies should be initiated on older children, to the extent feasible, prior to including younger children or infants.

Drug research studies may be considered ethically permissible when they can be shown to have a potential benefit to the individual child or provide generalizable knowledge. The evaluation of benefits should take into account the importance of learning about the disease process or the biologic function, providing innovative treatment for the subject's own benefit, and the child's satisfaction that he or she has contributed to the study of childhood disease or biology of children.

Drug studies that promise no demonstrable benefit to the child in the study or to children in general should not be conducted, irrespective of the attendant risks.

The risks to be evaluated should include the known and predictable effects of the drug, as determined from prior animal and clinical studies, and the risk of the procedures employed in the study. The risk of procedures that may not be of concern to adults but are to children include discomfort, inconvenience, pain, fright, separation

from parents or familiar surroundings, effects on growth or development of organs, and the size or volume of biologic samples to be taken.

In conducting JRA research, particularly new agent research, the relations of the risk should be justified by the anticipated benefits to the subjects. In other words, children should not be exposed to a potentially toxic agent if no anticipated benefit is expected.

This raises a question about their involvement in phase one research. Although there is the hope that the child subject will benefit from inclusion in such studies, their principal purpose is to learn about the drug's action. Obviously, the more likely that the child's disease is life-threatening or severely debilitating, the greater the ethical justification for including him or her in these kinds of studies.

However, in any of these trials, it is very important that the participating families understand that the purposes of the phase one trial is principally to study the drug's metabolism and to profile its toxicities, and even though the agent under study may ultimately be found to be active, the dose a particular child receives in a phase one study may not be an effective one.

Finally, I would like to comment on the use of

placebo controls in randomized controlled drug research in JRA. The Federal regulations allow approval of research involving adults that bears risks but does not afford benefit to the subject, the reason being that as autonomous agents, their considered judgment must be respected even if the outcome of their decisions bears risks and does not benefit them.

However, because children are less capable of self-determination, they must be protected to a greater extent than adults. Consistent with this ethical requirement, the children's research regulations are more restrictive. According to the regulations, research on children can only be approved if it falls into one of four categories. The categories are constructed on the basis of the degree of risk and the prospect of direct benefit of the research.

IRBs can approve research in the first category, which involves no more than minimal risk. Minimal risk means those risks that might occur during daily life of normal children. The National Commission suggested that in children, that would include physical examinations, weighing, measuring, urine collection, immunizations, blood drawing, and the performance of simple psychologic tests.

Because of the toxic quality of the drugs utilized

and the risk this entails, it is unlikely that this category is applicable to most JRA drug research.

Most JRA randomized drug trials are more likely to be classified in the second category, which involves greater than minimal risk and presents the prospect of direct benefit to the individual subject. In this category, the relation of the anticipated benefit to the risk must be as favorable to the subject as presented by available alternative approaches.

This means that each and every subject must have a reasonable prospect of deriving an acceptable level of direct benefit from participating in the study. This indicates that any randomized clinical drug trials on children with JRA would require either active controls or at least so-called background therapy but not inactive placebos.

A third category does exist that also involves greater than minimal risk but without prospect of direct benefit. In that category, the intervention or procedure should be expected to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder.

If placebo controls are proposed for use in JRA

randomized drug trials, it is unlikely that these drug trials could be determined to be in this category because some of the subjects would receive an agent expected to offer benefit.

A final category includes research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Approval of research in this category involves a determination by the Secretary of DHHS in consultation with a group of experts. While this approach is available, it is cumbersome and is unlikely to be used on any regular basis for JRA drug research.

In summary, in order to afford children the maximum protection and the greatest benefit in most randomized trials, the use of inactive placebo controls would not be ethically acceptable. However, an inactive placebo trial could represent an ethical approach if there are few or no data from adult studies about the efficacy or the risks of the investigational study or if the agent has a novel mechanism of action or if it represents a new class of drugs.

So I might modify that by saying that, usually, placebo control studies are not ethical. However, I would say that in such instances, one would have to provide strong

justification for the use of placebos, and in such instances, the investigator must help the parents and the subject understand the importance of the control trial, the comparative benefits and risks of receiving active treatment in comparison to a placebo, and that the active treatment may, in fact, prove to be harmful. Thank you.

DR. MILLER: Thank you very much.

Would anyone like to comment or ask questions at this point?

CRITICAL RESPONSE/GENERAL DISCUSSION

DR. MAGILAVY: Sandy, from the perspectives of invasiveness of clinical trials, as well as obtaining consent from parents or assent from children, do you see a distinction between potentially severely disabling diseases, such as juvenile arthritis, versus potentially lethal diseases?

DR. LEIKIN: Do I see a distinction?

DR. MAGILAVY: Right.

DR. LEIKIN: I really can't answer that question because I don't have that much clinical experience with JRA, but I would say from what I just learned in the last couple of weeks, I'd say it sounds like a pretty--I would say that there isn't any difference. That's my gut feeling. I would think that something that is so chronically debilitating is

as bad as something that's life threatening, but that's controversial.

DR. GIANNINI: I personally think we've done our last placebo controlled trial in kids, especially with the agents that we're interested in testing and especially with a study that's any longer than three months. If we now can take advantage of our colleagues in Europe, which we hope we can, then it's even going to be more difficult.

I just do not see us doing any more placebo controlled studies in kids. I hate to be so blunt about it, but I've seen several failures now because of the placebo design and under--you may say that it may be ethical. I'm not sure it's feasible, especially if we're talking about a phase two or a phase three trial.

DR. JOHNSON: That may be the difference. There's an assumption floating around, I think, that use of placebo implies withholding known active therapy, and if one doesn't imply the other, then there may actually be settings where you have to use a placebo control, and I'll give you an example.

If you have an early agent that's been tested in animals and a few adults and it looks nasty but promising and you want to start experimentation in kids, what patients are you going to use? You're going to use those who failed

all active therapy. My reading of the ethical literature, and if you look at the Helsinki and the Nuremberg Accords, that's what drives this sort of stuff, and what drove those were really sort of gross violations of the Hippocratic perception of medicine and that perception of medicine is doing no harm and obviously not withholding any known active therapy.

So it's very hard to withhold active therapy, period, even in the adult setting, and that's the reason for people being upset about even using flare designs for non-steroidals. But it's a different story if you've got an early agent that may well be toxic, and if it doesn't work, then you would have been better off on placebo than on the active drug.

DR. STRAND: Or what about the other model, which is sort of the AIDS setting where we've learned two other designs and one of them is that you leave the patient on the failed agent and you randomize them to receive either placebo on top of the failed agent or the new agent in combination which hasn't been tried before, the cyclosporin study?

DR. JOHNSON: That's what you have to do in this setting. You have to keep them on methotrexate and add the drug.

DR. STRAND: The other situation would be that you do two active controls and a placebo arm, and after a defined period of time, like three months, which is the most you would ever study somebody, they're allowed to leave for defined lack of benefit and they would have already been randomized to receive the opposite active therapy, or if there were a placebo, one of the other two active therapies, so that they only had three months of observation time that we required without benefit.

Wouldn't those still be ethical, because in many situations now with adult RA, we actually can't do anything further than that kind of a design because the IRBs say to us that placebo is not ethical.

DR. GIANNINI: I think that if there is the promise of crossing over to active agent, then we'll do a little bit better job in terms of finding patients, of enrolling patients. But the straight parallel study, once randomized, always randomized--

DR. STRAND: I don't think any of us think we should do that in any autoimmune disease--

DR. GIANNINI: Right.

DR. STRAND: --once we have an agent that has some whimper of benefit demonstrated.

DR. JOHNSON: You can't ethically withhold drugs

to a major degree. I mean, I suppose if you were a rheumatoid, you could withhold methotrexate for a few months, but if you have a drug that you've got some sense of activity already in the adult or in the pediatric setting, then it's very problematic about giving placebo and you're going to have to get into the active controlled designs.

Now, there's an ethical argument against that, because the number of patients you need to show efficacy to an equivalent degree of reliability is a lot more--

DR. GIANNINI: It's high. It's high.

DR. JOHNSON: --and if your drug proves to be inferior or not work, then after the fact, there would have been a huge ethical argument against doing exactly the designs that you thought you could only select ethically at the outset. I mean, it's sort of paradoxical, but--

DR. GIANNINI: Yes. We've had a number of those trials already, Kent. The best thing we did was give them placebo.

DR. SILVERMAN: You addressed something that maybe is ethical and that was that you can't get enough patients. Is that what you were implying? There are two issues. One is if you're on methotrexate, and as a background medication, I don't see how that would be contraindicated or ethically immoral to add in a placebo control trial to that

background medication. But what you were implying was those days are numbered because maybe it's unethical to enter placebo control trial because it's doomed to failure by enrollment numbers.

DR. GIANNINI: No. I was saying that even if it is considered ethical, as he just stated, that I don't think it's feasible.

DR. JOHNSON: Yes. You have to separate the two, though. It may not be feasible, and in the adult world, all the academic centers say it's impossible because they never see patients who are off methotrexate. Now, I've gotten mixed feelings back from the pediatric people here. Some of them say that the non-pediatric rheumatologists never start kids on methotrexate, and others say they frequently do. But it's a big problem if the latter is true, because then you've got a crew from primary physicians, not pediatric rheumatologists.

DR. SCHWIETERMAN: I was just going to reiterate the point that Kent has made, eloquently made, that there is a distinction between withholding standard of care, which no one at the agency, I think, and the ethical community agrees should be done, and treating with placebo.

I would argue that placebo controlled trials are not only ethical but they are essential to the development

of this field, provided that those patients on placebo, A) get the standard of care at the beginning after randomization, and B) after a certain amount of time have the option of receiving the arm. But to endorse non-placebo controlled trials absolutely without respect to these definitions, I think is to set the field back, given the high placebo rate in patients and given the nature of this disease in general.

DR. WALLACE: It seems to me that the two places where the studies are going to kind of have their greatest impact is, one, of course, is going to be with the desperate patients in trying some of the newer agents, et cetera, and then the second is going to be at the point at which we would put a patient on methotrexate, they get randomized. They either get methotrexate or they get the new agent we're trying to look at.

That seems to me, with most of the drugs that are sort of coming out, where studies are going to be. Dan is shaking his head. Maybe it's going to be a patient who you're starting NSAID A versus NSAID B. I don't know what--

DR. MAGILAVY: I'll turn it back to you. If you had a patient with active severe polyarticular disease and you had the option of putting them on methotrexate, knowing that there's a high probability that it won't work, would

you be willing to try a new agent which has no known proven efficacy and not understood toxicity?

DR. WALLACE: Of course not. Had it been shown in adults and looked very promising in adults, then I'd be very interested in trying it.

DR. MAGILAVY: How about early on, early on in the stage of development?

DR. JOHNSON: I don't think you're talking about early on, are you? You're talking about later, sort of pivotal trials, aren't you?

DR. WALLACE: No. No. No. I'm talking about after drugs have gone through--

DR. MAGILAVY: After adult studies.

DR. WALLACE: --all the adult studies and have looked like they're going to work. I don't think anybody's talking about using studies right out of the--

DR. JOHNSON: They're all ethical decisions. Anytime you randomize, you have to have--Pito [ph.], who is a big spokesman on this, calls it the uncertainty principle. You've got to have substantial uncertainty in the patient's mind and in the physician's mind that there's no difference between the treatments. Otherwise, you can't ethically do it. You couldn't ethically participate. You shouldn't have your child participate. You shouldn't participate if you're

an investigator. You've got to have this eco-poise [ph.]. That's another term that's been used in the literature.

You're saying that there's an agent that's been shown in phase two trials and in adults and so on that looks like it's pretty good that you, as an investigator, would feel comfortable in randomizing, but that's later in development than I think you're talking about, Dan.

DR. MAGILAVY: Early on, right.

DR. HEPBURN: There's another trial design, too. You're making the assumption that the positive control here, methotrexate, is pretty safe and it's efficacious, but suppose this were lupus and your positive control is psychophosphomiate [ph.]. You could go in with placebo and your drug there and your drug might have a sparing effect on another compound that's more toxic, and that's another type of placebo control trial.

DR. LEIKIN: Can I ask a question? Is there any evidence that a drug that is active in children is not active in adults in JRA? The reason I ask that question is one of the things that spurred the field of pediatric oncology was the fact that the kids were responsive to these agents where the adults were not, and so there was a lot of support and encouragement to go on. Is there any evidence that that's the case in--

DR. WALLACE: I think the--not directly, but what there is, is that kids appear to tolerate methotrexate much better, tolerate much bigger doses, and, therefore, I think at least I'm getting much better complete response rates than in adult patients.

DR. GIANNINI: Sandy, it's usually the other way around in terms of response.

DR. MILLER: Why don't we take a ten-minute break.

[Recess.]

METHODOLOGIC CHALLENGES IN JRA DEVELOPMENT (I-IV)

I. INTRODUCTION

DR. JOHNSON: In the interest of time, I'm not going to say anything, because I've already spoken too much, I think. Most of the comments that I wanted to make, I've already covered. I was going to talk a little bit about center effects and this or that, but I think that's kind of a diversion from the more important things we have, so I'm going to move on.

DR. NEUNER: I guess that means I'm next. The first speaker of this late afternoon session will be Dr. Suzanne Bowyer, who will be talking about prognostic factors and stratification needs for JRA clinical trials. Following her presentation, we will have the open discussion by the guest panelists and then it will be opened up to the general

audience.

II. PROGNOSTIC FACTORS/STRATIFICATION NEEDS

DR. BOWYER: Thank you. I'll try to incorporate into this talk, which I have put together already, all of the comments that have been made already and the comments that Dr. Wallace has been slipping me all day on what I should be saying.

Anyway, I was asked to talk about prognostic and stratification criteria, and the problem is, as Jim Fries said in 1994, that good prognostic criteria sets are clearly needed, especially for RA and SLE, but have not yet been developed because to do so requires access to longitudinal data sets, determination of sensitivity and specificity of proposed criteria, and we really have not done this for adults or pediatrics. Therefore, we're a bit handicapped.

However, we have to start somewhere, so I propose that we start with how has this issue been handled in previous drug studies. I looked at the literature of every outcome study in JRA that I could find and read. There were a few in German that got away from me, but I tried to do most of the others. Then I'll make some recommendations along the way and then a summary of recommendations for people to comment on.

First of all, how has this been handled in the

past? Ed said that other people have done research along the way, but I don't think anyone has been organized into quite as large an organization as the PRCSG. So that's really what I took as a guideline.

In 1982, Dr. Brewer and Dr. Giannini presented their protocol for doing drug studies and they looked at these variables for each patient. Now, they did not stratify the patients, but these variables were all listed and could be used at the time of analysis if they wanted to look at something in more detail. So that's what's been done in the past.

In reviewing the literature and all the outcome studies that are listed there for you in the handout that I put together, it seemed that candidate prognostic factors were divided into several areas, patient variables, disease variables, laboratory variables, and a couple of medication variables, so I'll try to address what people have said about these in the past.

First of all, should we stratify by age? The earliest prognostic study was the one done by Colver in 1937 and he felt that death was most common in the younger children. Jeremy in 1968 felt there was a worse prognosis with a greater age at onset. Svantesson and her study in 1983 felt that prognosis, again, was worse if they had onset

when they were very young.

Ansell in 1959, you had a worse joint prognosis with age, but she was wise enough to suggest that was probably secondary to the fact that positive rheumatoid factor occurs in this group and that it's probably more the rheumatoid factor influence than the age that's causing them to have worse prognosis.

Laaksonen in her huge study, which to date has not been duplicated, over 500 children followed over 20 years, found no difference in those who had young and old onsets, and Anne Marie Prieur in 1984, looking at systemics only, found that there was no difference in age and onset.

So to summarize, there's really no clear influence at this point of age on prognosis. The ages of patients, I feel, should be listed in studies, but I would not use it as a stratification variable.

Patient's sex, Laaksonen in her large study found that boys, in general, did better than girls. In 1982 in Belgium, Dequecker found boys had a better prognosis. Andersson Fare and Fasth in 1995 in that wonderful article we've all been referring to today again felt that girls were likely to do worse. Barbara Ansell actually in 1959 said there were no difference in prognosis between sexes. I hadn't seen that she'd refuted that since then, but

everybody else--many other people feel there was a difference.

The two large Scandinavian studies showed a difference in prognosis with sex. Multiple others have not commented on this. Whether they noted it or not is not clear. I would probably list the sex of the patients, but I don't think there's enough evidence that we should stratify boys and girls.

The duration of disease prior to treatment is important. In a couple of very early studies, Edstrom and Ansell in the 1950s and then Laaksonen in the 1960s all felt that patients treated within one year of onset did better than those whose treatment was delayed, and I think that's so well established, nobody ever bothered to address that any further.

Most people nowadays are referred within the first year of their diagnosis. People are savvy enough to do that. Now, with HMOs coming on the scene, we may see us go backwards to patients referred after four years, but hopefully not that bad. Anyway, I hope this will not be an issue in future studies.

Disease activity--several investigators have all agreed that JRA continuously active longer than three years predicted a worse functional outcome. In 1969, a study from

Cleveland Clinic, Pazirandeh was the lead author, said persistent polyarticular inflammation is a worse outcome. An Italian study in 1994, the worse response to methotrexate in systemic occurred in patients who had longer than two years of active disease. And again, the big Scandinavian study, continuous disease activity is the best predictor of poor outcome. So we would like them not to have continuous disease activity.

Jeremy was the one who disagreed with that. He felt that prognosis of patients with greater than three years of activity was no different from those with less, and Ruperto, who is working with Ed Giannini in their joint study of Cincinnati in Italian patients said that the articular severity score, in other words, how bad their disease is at onset, was the best predictor of long-term disability.

So there's certainly an influence of disease activity on the outcome. The longer the arthritis is active, the more damage is done to the joints. Hopefully, patients are going to be treated early in their disease course and the duration of active disease won't be relevant to drug testing. It would certainly be reasonable to list the articular severity score at onset as part of the variables we're looking at.

Now, disease onset type and course. I think we've already agreed that these are different, but I'll run through the literature anyway. In 1952 and 1958, systemics did worse. Is everybody surprised? Calabro found that monoarticular onsets did the best. Multiple investigators found that Paucis did better than polys and they all did better than systemics.

Dequecker found that polys do the worst. Prieur said systemics who have a poly course do the worst. David found that extended Paucis do worst of all. In other words, his feeling was that if you start with Pauci and then convert to poly, you have an even worse prognosis.

The Scandinavian study, conversion to the polyarticular course predicts worse prognosis. Giannini and Ruperto in 1996, using the CHAQ, found that Paucis did better than polys but the polys were about the same as systemics, and Chet Fink was the latest in many authors to point out that JRA subtypes differ from each other clinically and genetically.

Other points to consider that have been brought up already, the unusual response that systemics have to medications. As pointed out earlier, Gare and Fasth pointed out that many of their patients, one-third of their patients, changed disease patterns during their courses.

And, of course, subset definition is evolving and may not be the same in the future.

My thoughts are that the three disease types are very different in their onsets, but following a polyarticular course seems to be the common factor leading to a poor outcome, so I think we need to talk about both disease type and course and consider that in analysis of the patients in drug trials, and I'll expand on this a little in my summary slide.

Patients with active systemic symptoms should be differentiated from the others. They are going to need frequent clinical and laboratory monitoring at the very least, and consideration should be given to special guidelines in trying new medications on this group of patients.

Which joints are affected? A considerable amount of evidence suggests that small joints affected first, suggests that they're going to do worse. Hip involvement also will lead to a worse functional outcome. Here, the early involvement of small joints, as is seen with polyarticular JRA, seems to predict a worse prognosis.

Again, the polys are the ones who have the worse functional outcome, so I would note the involved joints in any drug trials. That will be done, I'm sure. I don't

think we should divide them into stratification variables more than we would already by saying they have a poly course.

Functional capacity--actually, the only clinician to address this in the literature was Ansell back in 1959, and she used the old Steinbacher classes and noted that no matter how poor the patient's functional capacity was at onset, they all got better, and we've all seen kids come in and they're terrible and they can't even move and they have to be carried into your office and they walk out a week, a year, whenever later, but they all get better. So I think the functional capacity of patients in drug trials should be noted in order to follow their improvement, but I don't think you can stratify using it.

How about laboratory variables? WBC has been proposed by some authors. A couple of very early authors felt that a WBC over 25,000 predicts a worse prognosis. Well, I think nowadays we can summarize that by saying these patients probably had systemic disease.

Laaksonen in 1966 found that anemia early in the course predicted a worse outcome. Again, this probably is associated with systemic disease, as are the platelets that Rayful Schneider, et al, looked at in the systemics. So systemic disease is associated with worse outcome.

The SED rate has been talked about by several authors but using different guidelines. Lindbjerg in 1964 used SED rate greater than 100. That predicted a worse outcome. Laaksonen and Dequecker used SED rate greater than 30, and Ruperto and Giannini in 1996 said that the SED rate greater than 20 is a weak predictor of decreased functional capacity. So everybody agrees that the higher your SED rate, the worse you're going to do, but again, it would be difficult to separate that from the fact that these were probably systemics in the beginning.

ANA--no author has mentioned that a positive ANA is a bad prognostic factor for the joints. In fact, Barbara Ansell said that the ANA patients tended to have a good outcome from their joints and the main disability, if it occurred, is from eye disease, so the ANA certainly can predict a bad outcome from the eye disease but may not be the best thing to follow in terms of joint disease.

Rheumatoid factor, I think several people would agree, is going to have a worse outcome and they probably ought to be put in a different category. X-ray changes, multiple people have noted that early x-ray changes mean a poor outcome.

And as far as genes are concerned, this is controversial and will probably generate some comment. The

Cincinnati group, Catherine van Kerckhove, et al, have noted that certain genetic polymorphisms predict a worse outcome. She did two papers that actually have been published, and there may have been more in abstract form, but the ones that are actually published, this one said that patients who have the Pauciarticular converting to polyarticular course tended to have this genotype. The problem is, there are 19 patients who were Pauciarticular converted to poly and only 11 were positive for this particular marker, so I'm not sure it's 100 percent in predicting.

The other paper that she published was in Iritis, therefore, I didn't summarize it, and they did find that a similar marker predicted a worse outcome for the eyes.

Can any of these laboratory variables be used as prognostic or stratification factors? I think that the rheumatoid factor positive patients need to be grouped differently. They clearly have a worse outcome in multiple studies and I think they need to be separated out.

Although early x-ray changes seem to predict a bad prognosis, Dr. Poznanski showed us very nicely how children can change their x-rays, heal their erosions, develop erosions, all of which are based on the fact that they have thick cartilage. This may not be something that we can use as a prognostic indicator, or a stratification factor,

rather.

The rest of the laboratory tests, I didn't feel have been consistently shown to be prognostic indicators, and in my opinion, genes are too new on the scene to be useful at this time, except for maybe HLA B27 and DR4, which goes along with rheumatoid factor.

Not all of the genes have been identified yet. Including them is going to add greatly to the cost of any study, so all of these have to considered as we think about whether to use genes or not.

I was also asked to address the issue of response to previous medications. There's very little in the literature about this. The Cleveland Clinic study in 1969, poor response to medication is a bad prognostic sign, and Carol Wallace picked it up again 22 years later and said, yes, we should look at this as a bad prognostic sign. I think all of us would feel that non-response to medication, multiple medications, is a bad prognostic sign.

So my recommendation would be that poor response to previous medications should be considered a bad prognostic sign and that children who have failed methotrexate versus children who are unable to tolerate methotrexate and therefore are being considered for an experimental drug are probably in a different class and I

think these probably should be separated out if they failed to respond to methotrexate.

Corticosteroids--what do you do about patients on steroids? Patients who enter trials of new JRA treatments will have failed multiple medications. Most of the systemics, I suspect, will be on steroids and this will be necessary in order for them to function. Therefore, the goal of trials may need to be stated in such a way as to allow tapering of the steroid dose, which shouldn't be strange to anyone in this room because we do that in lupus all the time. This concept actually was already suggested as part of the 1995 draft guidelines, so I would suggest we just stay with that rather than doing something different.

In summary, I would agree with what people have been alluding to at the front table here all morning. Because of the limited number of patients available for drug trials with JRA, pre-trial stratification is not a reasonable option. You're going to cut off your number of patients. However, patients with active systemic disease need to be separated out because they can get into big trouble with new medications.

However, I would like to see the following patient groups analyzed differently. The main thing here is to consider their course, and these are my suggestions of how

we split them out, but they are open for discussion. Systemic onset, poly course; systemic onset, Pauci course; the systemic onset systemic course is already separated out; poly onset, poly course; and Pauci onset, poly course. My feeling was at the time that most of us would not be doing experimental research on Pauciarticular when most of them respond well anyway, but if we do use something comparable to--what are we calling it now, system-relieving medication, then we'd include the Paucis there as Pauci onset, Pauci course.

I think the rheumatoid factor positive patients should be separated out, and whether the patient was a non-responder to methotrexate, I feel should be separated out. Thank you.

DR. NEUNER: Thank you, Dr. Bowyer.

This topic is now open for discussion by the invited panelists, followed by the general audience.

CRITICAL RESPONSE/OPEN DISCUSSION

DR. JOHNSON: Speak up to the microphone so that people in the back can hear the questions. All the microphones are on. You just have to get close to them.

DR. SCHWIETERMAN: Thank you. I just had a question. That was a very informative discussion, but it was unclear to me what you meant by the different subgroups.

Would those be stratifications? Would those be inclusion criteria, in your estimate, or would there be certain other protocol considerations that you would put into a study? How would these things be divided, in your mind?

DR. BOWYER: The groups that I listed?

DR. SCHWIETERMAN: Yes.

DR. BOWYER: I would suggest that when the data is analyzed, that these people be separated out.

DR. SCHWIETERMAN: I see. So as subgroup analysis?

DR. BOWYER: But I don't think you can ask for this many Paucis converted to polys or systemics converted to polys because you're just not going to get the study done.

DR. SCHWIETERMAN: You see, this is an important point, I think, because of the numbers of patients in the country and how you would define, then, efficacy based upon this analysis. But you would recommend that this be done as part of the prospective analytic plan in the beginning for each of these subgroups because of their potential different responses to therapy?

DR. BOWYER: Yes, I would.

DR. CASSIDY: Let me make a comment on what Dr. Bowyer just said about the polyarticular course. In the

1986 study on prognosis in relation to course subtype, the three course subtypes that did worse prognostically were the polyarticular patients who were rheumatoid factor positive, the Pauciarticular patients who became polyarticular but were not rheumatoid factor positive, and the systemic onset patients who became polyarticular who were not rheumatoid factor positive, and our conclusion from that study, as I'm sure you remember, was that it didn't seem to be that the rheumatoid factor was the controlling element but rather the polyarticular course, which Sue, just simply reinforces what you've already said.

May I ask a question, Kent, because this business of rheumatoid factor has come up so frequently, and we have heard here that we should be careful about transporting information determined from studies of rheumatoid factor rheumatoid arthritis adults, factor positive adults, to children who are not rheumatoid factor positive.

Certainly, if we are doing drug studies in a tertiary care center, most of the adult rheumatoids, I would assume, are going to be rheumatoid factor positive. Is that information determined, then, transportable to the private physician in his clinic where I would assume even today that most community-based rheumatoid arthritics are not rheumatoid factor positive?

DR. JOHNSON: If you're asking, has there been a generalization problem in drug developments in adults that target rheumatoid factor positive patients, most development programs tend to not do that. I mean, there are ACR criteria, but you don't have to be rheumatoid factor positive to fulfill ACR criteria for rheumatoid, I don't believe.

DR. CASSIDY: No, but the fact is that most of the patients in tertiary care centers where a lot of these studies have been done, except for those of Fred Wolf, would be positive.

DR. JOHNSON: We have not made it an issue that--we have not perceived that generalization as a problem in that setting. In fact, we may hear shortly that extrapolation to at least the rheumatoid factor positive polyarticular kids may not be a problem, either.

DR. CASSIDY: Do we have data to show that it's not a problem in adults?

DR. JOHNSON: Extrapolating from the positives to the negatives? I think the general sense is that seronegative RA is not fundamentally different than seropositive RA. What do other rheumatologists in the room feel?

DR. CASSIDY: You know, genetically, it is.

DR. JOHNSON: I'm not sure that's definitively clear, either.

DR. GIANNINI: Jim--excuse me, Bob. In every one of our studies of DMARDs, we've looked at the rheumatoid factor positive versus the negatives. Now, while you can't do anything statistically about it because the number of positives is so small, there hasn't been much difference in terms of frequency of response.

Let me clarify something that Suzanne had stated, and I think it's getting confused here. She talked about outcome, and in every one of those studies, including ours, we're talking about long-term outcome. The Ruperto-Giannini study that she cited several times, the mean follow-up was five years, so that the probability of response in a relatively short-term clinical trial may not be influenced so much by, say, rheumatoid factor positivity as it is in terms of the longer-term outcome. So those things she showed you were longer term, five, ten-year outcomes, not short-term clinical trial prognoses.

DR. CASSIDY: As you know, Ed, the 1986 study looked at outcome at five years, so it was comparable, but, of course, it was not designed as a drug evaluation study.

I'm interested in your comments. Of course, there are a couple of other fellow travelers that go along with

rheumatoid factor seropositivity in any study. First of all, as Ed has said, in most pediatric studies, these patients are going to be too few in number to be analyzed separately, but they are the ones that are most likely to have rheumatoid nodules, rare as they are.

They're going to be older patients at onset, I would assume, nine years of age or older. And, I think there's also a relationship with duration of disease in rheumatoid factor seropositive in the pediatric age group, which is really quite a signal distinction from adult RA, where there is not an association with duration.

DR. JOHNSON: Rheumatoid factor positivity, particularly high titer is a risk factor in the adults, as are nodules and erosions and so on.

Maybe I'll just make a quick comment. You can choose not to stratify, but you do it at your own peril if you lose. If randomization throws you the wrong dice and your treatment arm gets all the tough patients because they've got nodules or rheumatoid factor positivity or whatever else you think is a risk factor, you may lose seeing a drug effect because you didn't stratify.

DR. MILLER: I think that there are differences in adults, genetically, clinically, and prognostically, but this is when you look at group data of large numbers of

groups and there are clear individual exceptions to that rule, obviously. The problem is, when you are a drug company trying to develop a label for an agent, just as Kent has said, you usually take the risk and you lump all these together, hoping that you won't have that randomization problem if you have a large enough trial.

So there's been, I think, a lot of economic issues that have driven some of the ways some of these studies have been done, myself, but I think there really are differences and there are many more subsets than we realize today.

DR. LIPNICK: Bob Lipnick, Washington. Sue, I just wanted to raise a thought, and that is in your breakdown, you didn't include in potentially new therapies to look at the kids, Pauciarticular onset that, in fact, follow a Pauci course. Certainly, there's lots of us who have, whether it's 20 percent, 30 percent of those kids who go on, don't respond to the non-steroidals and other therapies who have gone on to methotrexate. At least, I certainly do, and I know other people in this room have. So I just bring that up.

Are there other people in the room that have that experience? Obviously, it's the most common onset, and so should that group be included? Though the numbers aren't going to be huge, just because of the frequency of Pauci

onset, I think we ought to think about it.

DR. BOWYER: My comments are twofold. Yes, you could certainly include that group. At the time, I was thinking DMARDs and biologics and I didn't think that we'd be treating Paucis.

My question to you is, are you injecting these kids?

DR. LIPNICK: Yes, some of them. Some of them are injected if they don't respond.

DR. TUCKER: I have one comment about dismissing the idea of looking at functional capacity as a stratification criteria when you put people in trials, I guess. I'd be concerned that if you have a large group of patients and some of those patients are very severely affected at onset of starting this drug, in other words, they're in a wheelchair or they're really very poorly ambulatory or they're non-functional in other ways, again, are we going to be missing out on showing effectiveness of a drug if we pull those patients in with other patients who have a better functional capacity at outcome, because perhaps those patients already have some damage that's not going to improve and therefore their functional capacity when we measure it is not going to improve in this drug trial. So they're going to be non-responders when maybe we

should have looked at them separately from the start.

Since more severely affected patients are more likely to be put into experimental drug trials, I just raise it as a point. Sure, many patients will get better, but maybe some of them won't, and I think we should look at that.

DR. BOWYER: I actually think that's a good point, Lori. If the patients are entered early in their course, as Ansell was talking about, I think it probably doesn't make a difference because they all get better. But if they're entered after they've had disease for three or four years as we do the initial trials, that would make a difference.

DR. RIDER: Earl?

DR. SILVERMAN: When you enter somebody, is the stratification possible but in the analysis they become unstratified to get around this idea if you centrally randomize? So the idea is, all rheumatoid factor positives will be randomized separately. All Pauci to poly get randomized separately. Therefore, you alleviate this potential bias, as Kent pointed out, of all the by chance rheumatoid factor positive falling into one group, or is that an illegal statistical thing to do? I'll address it to Dan or Ed or--

DR. JOHNSON: No. You know, there's a balance, I

think, but there are certain--breast cancer has got about 60 factors that you can arguably stratify on. Obviously, that gets ridiculous, and we may be up to ten factors already here, and that's probably too many.

I don't have a good sense as to when you--I think the logical thing would be to stratify on the things which you think have the most potential for impacting the outcome. Then the other way you can do it is the things that you cannot stratify on because it becomes too impractical, you could agree up front in the protocol that these will be covariately adjusted for in the analysis.

But the underlying theme to a lot of this discussion is, is a trial of all JRAs going to be deemed credible--is an inference from a trial of JRA patients can be deemed credible for all three subtypes, and we haven't really directly hit that head-on. We're going to touch on it, I think, in a minute, because it's going to be easier, I think, for the polyarticular seropositives because the new pediatric guidelines allow us an extrapolation in that regard.

But if you have a trial of 100 patients and you do stratify and you get 33 in each and you do very well in your Paucis and very well in your polys but your systemics get worse but your whole trial succeeds, how do you interpret it

and how do you label it? That's the issue.

DR. WALLACE: I'd like to urge all investigators to be very thorough about looking at all the patients in terms of some of the HLAs that we could look at, the D2, the DR4, B27, in addition to the usual ANA positivity and rheumatoid factor positivity, not in terms of stratification but in terms of analysis, which I think in upcoming years then may help us to stratify, because I've been fairly amazed at how awful the disease is of patients who are ANA positive, and unbeknownst to me, but later on somebody orders some blood test or whatever, they come back B27 positive, in addition. They have horrible disease, just horrible. I've been struck by that in later years.

You may have some of those patients, too, Ross, but maybe you're smart enough to get them at the front and know that they're--but I was struck, though, with the Cincinnati data that was presented at the ACR meetings, how many of your true-blue polys who are actually B27 positive, more so than your normal population, and I think that's something we need to look at.

DR. ATHREYA: Two comments. One is on the duration. Just by the nature of the delay in the diagnosis and those are the kind of thing we heard about, wait for some of them to become Pauci to poly, then we'll need to

start thinking about some of those, and what Cassidy was commenting on, where the duration is an important thing you can't just ignore, need to consider.

Then the stratification on the numbers, my memory is in the co-set criteria that the ACR developed, ours is very similar. Didn't they say that the numbers needed in each arm, it's not really that big. It's like 25 or something, isn't it?

DR. JOHNSON: The numbers needed for what?

DR. ATHREYA: For each arm of that--stratified for each group, the way this co-set criteria was developed, it wouldn't require that large a number, am I not correct?

DR. JOHNSON: Well, yes. I suppose if you have a super drug, it might only take 25 patients to show it works. I mean, that's going to depend on the noise that you can minimize with your treatment and with your investigators and all that and how effective your drug is and how much noise there is in the drug response.

DR. SILVERMAN: Can I just make a point that Kent made? If you look back and you extrapolate what Kent was saying, if you would have, for argument's sake, gold would have been efficacious in RF-negative polyarticular JRA and we would have lumped systemics and that we would have had an indication for gold in systemic JRA, and I don't think many

people in this room would be very pleased today to have been part of a trial which would officially recommend gold in systemic JRA.

DR. JOHNSON: Excellent point, yes.

DR. SILVERMAN: I'm just carrying on. The point is, you really have to--even if it works in the whole, maybe we have to put caveats into it in the subgroups.

DR. JOHNSON: Well, yes, and the other way you can do it is you have to have some pretty hard-nosed deliberation up front about what the criteria for the test and success of the trial are, and maybe the systemics can't be expected to be as dramatic as the polys or the Paucis, but they probably shouldn't be allowed to deteriorate anyway.

DR. NEUNER: Moving on, our next speaker is Ms. Sharon Olmstead from CDER. She will be talking about relevant regulatory statutes, which is a euphemism for the new pediatric labeling regulations.

III. REGULATORY: RELEVANT FDA STATUTES

MS. OLMSTEAD: I'll be trying to answer some of your questions and maybe raising some new questions for you to think about.

I'm the project manager for CDER's Pediatric Subcommittee, so just to say up front, I am not a clinician.

I am more of a regulatory expert. So as I pose this information to you, bear in mind I'm going to rely on the experts at the table to answer more of the clinical relevance of the information.

The goal of the pediatric use section in the labeling was to provide instructions in the drug labeling for doctors and pharmacists to prescribe medicine for children. As many of you are very familiar, most drugs, a lot of drugs are being widely used off-label and it sounds from discussions today as if this is a disease in which primarily all the drugs are being used off-label.

In 1979, a regulation was provided that if a sponsor could come in and provide adequate and well-controlled clinical trials in children for pediatric indications, they would be given that in their labeling. The intent of this was to encourage good clinical trials in children. Unfortunately, it did not work out that way. The agency found that there were a number of problems with this requirement stemming from obtaining informed consent for testing in children where they were not going to gain any direct benefit. Also, there were problems with placebo controls in this vulnerable population.

The regulation in 1979 did provide for a waiver of this requirement. However, it was not clearly stated in the

regulation, so it was rarely used. In fact, I believe there were only a couple of occasions where this waiver was invoked.

Sponsors basically felt that the ante for this was too high and did not proceed with developing trials in children. We have some data to support that. In 1990, the American Academy of Pediatrics did a study of new molecular entities approved in the mid-1980s and found that 80 percent of those products did not contain any labeling or pediatric information, and, in fact, internally, we have followed up on that during the early part of the 1990s and found that that continues to be the case. We still only receive about 20 percent of new molecular entities actually have any kind of labeling for pediatric indications.

We proposed--in October of 1992, there was a proposal published to revise the pediatric use section, and then this became final on December 13, 1994. This proposal basically applies to currently marketed drugs, and that's an important distinction for people to understand, that we are not applying this directly to unapproved drugs at this point.

This proposal, or now final rule, calls for sponsors to gather pediatric information available on their drugs and they need to decide--the sponsor needs to decide

whether or not this pediatric information can be used in the labeling to give instructions for use in pediatric populations.

The Center, or actually, the agency is putting the onus on the sponsors to go and collect this information. In fact, there was a time frame given that they had two years. So December 13 of this year, we are expecting that if sponsors know of pediatric information on their drug, they are to be submitting supplements revising their labeling. To date, we've received maybe a handful, and this is of great concern both to the agency and to Pharma, who has even contacted the agency to find out how many have we received and do we expect an onslaught of supplements come December 13 and what are we going to do December 14 if we have not received supplements. That's not something I'm necessarily going to get into today, but it's just something to think about.

The effect of the final rule provides--the new regulation permits a pediatric indication to be based on adequate and well-controlled studies in adults with other information supporting pediatric use. So basically, it's going to allow for the extrapolation of adult data into children and to further on that.

The agency must conclude that the course of the

disease and the effects of the drug are sufficiently similar in pediatric and adult populations to permit the extrapolation from the adult efficacy data to the pediatric patients. There again, this is an area where we are going to rely on the sponsors to provide us this information to justify why they think it's similar, but it will be the agency's decision. The individual review divisions will be looking at this and will be relying on the clinical expertise to make that final cut.

The extrapolation of the adult data, if it's adequate, then we would also need pharmacokinetic data, as well as some safety data, pharmacodynamic studies, and other data to support the safety, and that's basically the important part of it, is that the clinical information would then be coming from the safety end of it.

One of the points that I did not make in the previous slide is that not only do you have to show that the disease is similar, the course of the disease is similar in adults and children, you also have to show that the drug effects are similar, and that's where there may be some problems with some of your younger patients and whether or not they can metabolize the drugs sufficiently to provide the same therapeutic benefit the adults would gain. So that's where some of these safety studies would come into

play. They'd help you decide that.

The final rule does permit specific pediatric indication supported by adequate and well-controlled studies in the pediatric population, so we do not change--we still are encouraging that you develop clinical trials in pediatric patients. This simply provides for an extended use of the pediatric section and will allow for the currently marketed drugs that are being used widely off-label to come in and get the labeling, get the dosing that the doctors need for this population.

To take one step beyond this, I'm just going to describe very briefly, CDER developed a pediatric plan two days after the rule was proposed to try and address some of the other areas in which pediatric labeling, pediatric drug development may be falling short. The focus was on the attention for pediatric patients throughout the drug development to determine for each drug if studies are needed in the pediatric population, which studies are needed, and when they are needed and how to get them done.

What the Center has been doing to that end is with sponsors, we've been meeting and trying to interject that these various areas, where they are with their pediatric development and trying to get some feedback from them, and this starts back as early as their pre-IND meeting, before

they even come in with their clinical trials, and then it goes through the initial IND and then IND annual reports.

Then we continue through at the end of phase two meetings, as well, if the IND goes to an FDA advisory committee, which is somewhat rare. Generally, that's more the NDA phase. We also are working with sponsors at the pre-NDA meetings, as well as NDA submissions and our FDA 45-day filing, and then finally at the FDA advisory committee.

At that point, though, we're down the road to where we're started to consider, can this drug be used--can the rule be applied to the drug, and, in fact, we've had a couple of submissions where the disease is sufficiently similar and divisions have said that we will apply this rule once your drug is approved. You simply need to come in with a supplement revising your labeling and providing the essential safety data to support it.

That's all I have, and I hope that kind of answers some questions. There were, in the back of the table, there was the recently published guidance for industry on how to submit supplements to address this labeling revision, as well as the pediatric final rule, so that'll help.

DR. NEUNER: Thank you.

This topic is now open for comment and discussion.

DISCUSSION

DR. GIANNINI: I have a comment. This might be a good time to remind everybody that the FDA does give grants for studying orphan products through the Office of Orphan Products Development. The Collaborative Study Groups had two of these grants previously, and, in fact, we had a priority score good enough to do a third one in DAB 389 IL-2, but we ended up not doing that.

But if cost is a factor here, or expense for a no-market drug, these grants run $100,000 a year for up to three years for phase one, phase two studies, and then, I think, $200,000 per year for phase three and phase four. JRA, of course, is an orphan disease, meaning the overall prevalence of it is less than 200,000 in the population within the U.S., so these grants are available and not fairly easy to get, but they're there. You can get them.

DR. RIDER: Just to make a comment on the application of the new pediatric reg to JRA, the agency has considered the applicability of this regulation, and since it's been well demonstrated that rheumatoid factor positive poly JRA is identical to adult rheumatoid arthritis, that studies of efficacy from adult RA could then be used for that subset of JRA. However, pharmacodynamic and safety studies would still have to be done in that subset of

patients.

DR. JOHNSON: What would be the pharmacodynamic study? I don't know the answer to that.

DR. NEUNER: All right. For our last section on the agenda today, ingredients to real world JRA developmental programs, we have Dr. Bonnie Hepburn, Dr. Dan Magilavy, and Dr. Dan Lovell talking and sharing their thoughts with us on this area.

IV. INGREDIENTS TO REAL WORLD JRA DEVELOPMENTAL PROGRAMS

DR. HEPBURN: Thank you. I think it feels as if the appropriate salutation here is "Good evening" at this point. I think that many of the issues by this time have been raised, and I hope that means that we can move fairly quickly through them.

You might note the header on all of my slides, which reads "issues for drug development for pediatric rheumatic disease". I know that we're here discussing JRA today, but as one of the last speakers, I took the privilege of not only trying to bring together what has happened today but to look forward to doing the same sort of thing, or at least taking these same considerations into the other rheumatic diseases, because in many instances, the questions and the problems are the same. JRA may be one of the worst

problems that we have in terms of getting homogeneity, but it's not the only one that we have.

Dr. Giannini started the session this morning by getting into the complexities of outcomes and responder index, and then he mentioned, well, of course the sensitivity and the specificity of these measures are all dependent on how good the drug is. Isn't that really the problem? The drugs really aren't very good, and if we're going to address that, we've got to talk about industry incentives for inclusion in pediatric patients so that industry is willing to proceed and to develop some better drugs for us to use.

So the old style incentive, really, was this sort of thing, maybe a regulatory incentive which says, though shalt do this in children. It works, to an extent, but it's so much better if the incentive is similar to those that industry sees for other types of drugs, and that means the opportunity to have an expanded base for recruitment of appropriate patients and often an expanded market once the drug is approved.

Of course, there are the industry disincentives, and high on the list really are liability issues. When I go forward to management and I suggest that we begin to include pediatric patients, this is the first issue that comes up.

We don't want to deal with this if we don't have to. I don't have the answer to get around that, but it's a very significant issue.

The other problem really is that it's not very attractive to do separate trials, particularly large, definitive, pivotal trials when there are small markets. Frankly, this is just a low-yield investment for the companies and that's an issue that's going to not go away very easily.

The next question here, are placebo control trials really necessary, is one that I think has already gotten attention this afternoon and probably doesn't need to be readdressed, but placebo controlled trials are a disincentive for industry as well as for patients. It makes recruitment more difficult. The trials have to be larger, and there are alternatives.

There are certainly blinded alternatives with positive controls and there are some open label alternatives, including variations of different types of randomized trials where there are two or more doses or two or more regimens and, as we say, the double-blinded trials with positive controls. I think most of us seem to be in agreement here today that there are a lot of ways to avoid the placebo control trials.

An issue that's certainly gotten a lot of attention here this afternoon is the generalizability issue. How generalizable is the adult disease to the pediatric disease? This depends on, I think, three major factors, the pathogenesis, the mechanism, and the manifestations, and they may be generalizable in one respect and not in others.

If the pathogenesis is different in adult and pediatric disease, as has been mentioned, it doesn't make much sense to go in to generalize and to combine and go in with an antigen-specific agent. On the other hand, if the pathogenesis is different but it's mediated by a common cytokine, perhaps you can go in with a similar agent and have a valid trial.

One of the bigger questions, though, has to do with the manifestations of disease, because you could have the same mechanism. You may have pericarditis and joint disease, both mediated by the same cytokine, but the outcome and the manifestation is so different than you then have a problem in looking at the different outcomes in the same trial, and we've talked about that, as well.

So what do we do when the outcome variables differ? That's the big question. What happens, of course, is the trial for all seasons, the multiple subgroups, the multiple outcomes, the responder indices, what can often

become a drug development nightmare.

When we see this sort of thing, I have to step back and say, do I really want to see this kind of trial? Do we really have to do this kind of trial? Might I not get more out of looking at 12 patients with iritis or 12 patients with pericarditis and being able to select the patients specifically for what I want to see in the inclusion criteria and look at a focused outcome on the other side, would I not learn more from that kind of trial?

Yes, we'd like to have the big trials. We'd like to have them well controlled. But if we can't do that, we can always revert to the minimalist approach, and I think that's what the final rule is really addressing.

If we can't do all things, then maybe at least we can merge the adolescents with the adults, as has been suggested for the polyarticular disease, and then do the PKPD in the small children, but we should try to do that, I think, in the context of the therapeutic trial, and this gets back to some of the ethical issues that were raised earlier. I have a hard time thinking about doing PK in children where the therapy isn't going to continue for long enough for the child to really get benefit from using the agent.

Then we come to what do we do with the trial

results in a trial that's something less than definitive and isn't always well controlled? You know, lots of times we learn a lot of things in these trials. I would like to see a little bit more of that appearing in the label.

This puts a big burden on the FDA, because it's easy to say, if you have a definitive trial and everything is well controlled, then that deserves to be in the label. What do you do with some of this open label material, or what do you do when your large randomized trial with the multiple subgroups has differing results in the different arms, as we just heard from Ed Giannini? Or maybe, in fact, your large trial with the multiple subsets, in fact, fails, but you had success in one of the arms. Wouldn't we all like to know that?

The information is so hard to come by that it's important that the information get in the label, not just for the company who may be trying to get the drug on the market, but it's important for all of us who are trying to treat these children and have way too little to treat them with. So every bit of information that we get is important, and I think we need the FDA's help in getting some of that information into the label.

I think there's not one answer to all of this. It's just a question of looking at the agent, looking at the

subgroups, and trying to do what makes sense, generalize when we should, split when we should, try to take the appropriate agent in in appropriate ways, and there are a lot of ways to do this and I think we have to be creative about it.

Then in closing, I've asked myself, what can the FDA do to help us? I think a session like this is very important. It raises awareness and gets us all talking and I hope it doesn't stop with the meetings. It really needs to go forward. It needs to go forward with the other rheumatic diseases, as well.

I think we need their help in encouraging and supporting industry efforts. Show us where we should come in. Show us when you think there are some shortcuts that we could take. Let's do this together. I think I need to go back to my management in the company and say, you know, the FDA is anxious that we include the children and they want to help us get through this. That's what management wants to hear in order to make the investment.

Then, as I have just mentioned, I think anything we can do here to expand the information that goes into the labeling would be an advantage to both the industry and to the people that have to use the drugs.

DR. NEUNER: Thank you.

The next speaker is Dr. Dan Magilavy.

DR. MAGILAVY: I want to thank the organizers for inviting me today to this workshop. I think it's been extremely valuable and it's served as a major step, I think, into drug development in JRA.

I must question, however, Dr. Rider's judgment in inviting me to talk about the real world. I think those of you who know me well might question my expertise and authority on reality.

[Laughter.]

DR. MAGILAVY: What I thought I would do is cover a few issues, and I'd like to break it down into these four. I'd like to begin most of this short talk in basically a negative mode, similar to what we've all heard today, especially emphasized by Bonnie, and that is, what are the impediments from a commercial trial design and safety aspects and doing drug development, especially with a new drug in juvenile rheumatoid arthritis, and then hopefully to mollify any pessimism, ask the question, is there any hope, and I do think there is.

We've all heard comments about the commercial realities. We are dealing with a very small market, and especially with breaking them down into the various subtypes. It makes it much smaller. On top of that, these

are expensive trials to do.

We've talked about--or actually, we haven't talked about formulation changes that may need to occur on an existing drug, which even though we might be using less drug, the actual formulation costs may make it prohibitively expensive.

There are also additional preclinical expenses that may be required, which I'll talk on later. And as Bonnie mentioned, liabilities, which maybe actually kill it for the development in JRA. And, again, pricing. How much can the drug company charge to recoup all the expenses required for its development?

I think the major impediment is the trial design. All these issues have been touched on earlier, and I'm not going to elaborate on any of these. We are dealing with a heterogeneous population. Can we generalize from one subpopulation to another? Obviously not, an issue raised by Carol Wallace earlier.

What about selection bias here? What patients would we put in here? Would investigators be willing to put in patients who may be responsive to known agents, such as methotrexate, or would we have to look at methotrexate failures, at which case we may miss a drug that may be very efficacious.

The other has to do, we talked not only from a placebo standpoint, but the requirement for concomitant meds, and the potential for toxicity of using these drugs with whatever new agent we were talking about.

Blood sampling, as we just heard from Bonnie, is a major issue. We're going to need to look at pharmacokinetic profiles, as was just mentioned earlier from the FDA, as well as pharmacodynamic analyses, and again, what PD markers we're going to use, I'll bring up later, but again, that's also suspect.

But there are going to be, especially if there are differences between children and adults, we really will need to look at this issue of pharmacokinetics, which often will require large amounts of blood.

The unpredictable natural course of the disease, which Dan and Ed had mentioned earlier, raises the other specter. What about sample size, as well as the endpoints? I think it's clear that, I think, Herculean hurdles have been cleared by the groups championed by the Collaborative Study Groups. But we're still not there, at least to convince industry, at least my management, that these are clean enough, and especially having to do multi-center studies.

Along with that, and I think which hasn't been

approached, what surrogate markers are we going to use in the early trial development? Andy Poznanski mentioned MRI. I think that's an excellent point in the earlier trials. Again, very expensive. It clearly could not be done in the large--just financially not feasible in the large phase three trials, if we're going to do those.

I think all of this adds up to incredible difficulty in dose finding, which we really are going to need to find out in the earlier trials. What's the acceptable dose to use? Can we extrapolate from adult experience? Maybe not, and we may be at too toxic a level or we may be at not an efficacious one. Patients may require more drug, as Carol had mentioned with methotrexate.

Then, clearly, we're talking here, I think, for most new agents, about long-term effects, hopefully remittive drugs that control the disease, and along with that, I think, is the major specter of safety, and I think this is where I have the most concern.

Again, can we predict from rheumatoid arthritis the toxicities? I'm not so sure, or from other pediatric diseases. Maybe those are a better way to look. Compounded by the fact that we may be dealing with novel drugs in children with a disease which is non-lethal--yes, which potentially is quite crippling. In any case, children will

have a longer life span and we may see toxicities appear much later on which were unsuspected.

How are we going to predict these? I think we clearly will need more preclinical data of an established drug. Should we look at doing animal testing in young animals and from that information can we extrapolate? Unclear with the developing immune system, although I think we're somewhat reassured that there really is not much difference in the older child. Whether that really--has that really been tested in a long-term chronic drug use in the older child? The answer is no.

And again, could there be unique toxicities here, both the mechanism-based, which would be true for both small molecules and biologics, but also non-mechanism-based? We all know the experience with theoflin, which has a different pharmacokinetic profile, and it well may be the case for both biologics as well as small molecules that there might be different clearance, different metabolism, different protein binding. I think all these add into a high risk and a large expense for drug companies to develop a drug targeted for children.

With all that in mind, can trials using novel therapeutic agents in children with JRA be done? My bias, and again, this is my opinion, with new compounds in which

JRA is the first indication, no. I think all of us here would agree with that, especially for a drug that's going to be used long-term-wise.

On the other hand, which is maybe a no-brainer, is that agents that are already approved for other indications, I think, yes, we should look at it for all the reasons that have been mentioned earlier, and especially--and not just in rheumatoid arthritis. I think we should look at other diseases, whether it's inflammatory bowel disease or other pediatric diseases.

We must, I think, have a good understanding of the safety profile from all fronts, as clinicians, as the drug companies from a purely Machiavellian standpoint of liability and expenses. We must have a good understanding. We need, as I mentioned earlier, we need more preclinical data from drug interaction, especially since many of these patients will probably be on methotrexate, and we're not going to be doing placebo controls, information with young animals, and, I think most important, long-term safety data.

So in closing, I'd say, yes, I think that new drugs can be used in juvenile rheumatoid arthritis. It's a major risk and I think it's going to take a lot of selling from people like Bonnie and myself with our upper management to do trials in children, but I think they can be done.

DR. NEUNER: Thank you.

Our final speaker of this panel will be Dr. Dan Lovell.

DR. LOVELL: Thank you for the opportunity to speak. I'm going to reverse the order of the questions that were posed to me.

One question was asked, are the hurdles too high for development of drugs in JRA? The next question was, current situations and current problems.

This is a recent study that was performed, or we just actually tallied the drugs that children with JRA were currently taking in five pediatric rheumatology clinics, and of the drugs on the list, the only two that are approved for the use of children with JRA are naproxen and tolectin, so that a large percentage of our children, as we all know, are taking drugs that are off-indication. The next slide, please.

This is a kind of historical perspective, and this alludes to the success of the earlier set of guidance materials for approval for drugs in children. The Collaborative Study Group had performed 25 prospective trials of therapeutic agents in JRA patients. Eighteen of those were NSAID trials, seven of those were second-line agents. In D-Pen/HCQ, in a phase two study. Auranofin,

we've done both phase two and phase three. Methotrexate, phase two and phase three. Gamma globulin systemic was phase two, and IVIG in polyarticular JRA was a phase one/two study.

From that trial experience, we've generated 25 peer reviewed publications and many more non-peer reviewed publications.

We've had--actually, Ed corrected me--there's been three approved grants from Orphan Products of the FDA, IV gamma globulin in poly JRA, methotrexate in JRA, and an approved project that was not performed which is DAB 389 in severe polyarticular JRA.

Again, I'd just like to iterate, from all this experience, all this work, using the old regulations and the small market, only two drugs were approved.

Current problems--everyone has alluded to the small population.

Halfway through the lifespan of the Collaborative Study Group, we experienced what I call NSAID burnout. The pediatric rheumatologists were tired of doing one NSAID trial after another and the decision was made that we were--unless an NSAID was clearly different than the preceding NSAID, based on adult data, that we would not perform any more NSAID trials.

The interesting thing is that industry, I think, came to the same decision about the same time independent of us, because we have not been approached to do an NSAID trial for at least the last eight to ten years by industry, so that this is not an area in which we get approached to ask if we would be doing a trial. That was not the case ten or 12 years ago, when we got approached to do more NSAID studies than we had investigators of interest, but the environment has changed dramatically.

Because of the small population and the size of the trials required, multi-center trials are almost inevitable in pediatric rheumatology. One of the questions that was raised for us is what problem does center effect pose in these trials, and I say it's an unanswerable question because never in the history of any of the collaborative study group trials have we had enough patients enroll from any one center that we can assess that issue. So I think it's still an unanswerable question, but it turns out not to be a big problem because we don't have a huge number of patients enrolled from one center and a small number from other centers.

A current and ever-increasingly severe problem is the requirement to develop multiple research contracts in the course of one of these multi-center trials. All the

participant pediatric rheumatology centers in the country, in fact, most of the pediatric rheumatology centers, period, in the country, are in academic settings, which means that we all are burdened with administrators who require, in addition to IRB approval, a research contract that has to go through the grants department of that particular institution. At the current time, Ed, Link, and I spend more time negotiating the research contracts than we do in developing the protocol. It's an enormous problem, and I don't think it's going to get better.

Written into that is an increasing insistence on research institutes that we do an institutional-based overhead payment that's usually much larger than drug companies are used to doing when they do trials with private practice orientations. Generally, drug companies will go by with ten to 15 percent of overhead, if they have to pay it at all, whereas increasingly, the institution is requiring that we pay an NIH-type overhead, which is 25 to 40 percent, and drug companies just won't accept that, for the most part.

Always, these trials have been, at best, break-even propositions. They're not big money makers for the investigators involved, and when you try to assess personnel needs and faculty positions based on trial income,

it's quite unpredictable. So it makes it difficult when you try to run a clinical operation and base very much of your work on clinical trial income because it's very unpredictable.

FDA grants have been helpful in some instances, but the turnaround time for FDA grants is really quite long in relation to the interest span for industry support for studies in JRA. Drugs come and go. Companies come and go. Oftentimes, in the two years it takes to write a grant, submit it, get it reviewed, and get back to the company, the interest has dropped.

In fact, in two of the three FDA grants we got, we had one fail because the company changed their priority of research interests after the grant got approved, and the second, the original company that was going to supply the product had changed their research priorities and so we had to find a substitute product from another company. So the orphan indications and FDA grants have some specific challenges in pediatric rheumatology in terms of time of turnaround.

I have some comments about the current guidance material that we were given to review, and first, I'd like to applaud the authors for expanding our ability to look at indications to include more than just signs and symptoms, to

prompt us to look at quality of life and arrestment of functional damage to the joints and the possibility for remission. I think those are very provocative topics and we ought to expand our thinking about how we can test drugs in JRA.

I do have some problems, however, because these guidance materials really make it unclear, for me, anyway, and I think for people in industry, as to how studies should be done in terms of the subgroups that are listed there. For example, is there going to be a different trial that's required for each subgroup, a separate indication, or if we do a study in polyarticular course JRA, is the indication labeling going to be limited only to polyarticular JRA?

I think it's going to become a more difficult issue because the new set of JRA criteria is really much more of a splinter-oriented criteria set than the current set, even. We have three subsets now, but the new criteria that are being considered really divide it up into even more groups, and so we need to address this issue of how we look at these subgroups in terms of their impact on indications and that sort of thing.

I think if we come out saying we have to do more trials because of the uniqueness of these subgroups, it's going to make the marketing interest of companies even

lower.

This guidance material has a very broad listing of extra-articular manifestations. This guidance talked about growth, uveitis, nodules, bone mineralization. It's very encyclopedic in the manifestations of JRA, but it's unclear how those more global complications from the disease would be rolled into a drug indication.

For example, are we going to be required to come up with drugs that will not only improve the arthritis but also, at the same time, minimize or avoid the uveitis? There's some uncertainty in these guidance materials because all these more encyclopedic lists are rolled together.

I think that's the end of my comments. But I think in review of these guidance materials, it actually sets the hurdles higher in some respects than the prior guidance material and certainly set the hurdle higher than the guidance materials that Ed, Bonnie, and I submitted to the FDA some time ago.

When you raise the hurdles higher than the existent standards, given the fact that our past indication approval record has been quite low, it makes it seem more likely that fewer studies will be done in JRA in the future, so I have some concerns about the impact of these guidance materials on studies--the likelihood of having studies done

in JRA.

DR. NEUNER: Thank you.

This topic is now open for general discussion. Any comments from anyone?

CRITICAL RESPONSE/OPEN DISCUSSION

DR. LINDSLEY: I'd like to ask Dr. Magilavy. Dan, do you see the age, particularly with regards to an adolescent group, differently than younger children? Bonnie sort of touched on that, but from an industry standpoint, are there more incentives if we, for example, looked at an adolescent group and avoided the younger group? They may be more problematic as far as compliance or something, but you get rid of, I think, some of the concerns that may be more applicable to young children.

So do you see that as any sort of advantage, if the PRCSG, for example, did any sort of adolescent studies, because they're a group that I think we've sort of eliminated or overlooked, and--

DR. MAGILAVY: Right. I agree with Bonnie. I think, yes, that would be an easier group to look at, probably. On the other hand, we may be missing the major groups of JRA in which I think we're all interested, and a new biologic or a new small molecule that acts as an immunomodulator may be very effective in one and not in the

other. I don't know. How do you--

DR. HEPBURN: I think with the other rheumatic diseases, we have actually an opportunity here with the adolescents, more so than with JRA. I'm currently planning a trial in lupus patients and I think--and am planning to enroll adolescent patients because the disease is more generalizable from adults with renal disease to adolescents with renal disease than it may be if you took all pediatric patients with lupus who fall into many different categories with different end organ disease.

So there are situations where I think it makes a lot of sense, and that's one of the examples where I think it's an advantage to the industry because it involves more patients in a difficult to enroll patient group. And maybe this will be true in myocytis or scleroderma or some of the other diseases.

DR. MAGILAVY: I'd like to ask Sandy a question. Do you think we could learn anything from our experience with the pediatric oncology group with some of the new immunomodulators and apply that to use in pediatric rheumatologic disease, from both a safety standpoint and potentially an efficacy?

DR. LEIKIN: I've not been involved with those agents, so I don't know.

DR. RIDER: I have a question for Dan Lovell. We congratulate you on the formation of the new Collaborative Study Group with North America and Europe and think that this will really greatly increase your basis to conduct clinical trials for JRA. Do you see that this group might seek regulatory approval of new agents to license in the United States and Europe?

DR. LOVELL: I think that's a possibility. In fact, for the European investigators, it's a very real possibility because they are in the process of thinking about submitting grants to the European Common Market and there's a mechanism there for funding drug studies at that level.

Now, the main purpose of forming this group, however, was to address clinical issues that we haven't been able to approach in the context of FDA or pharmaceutical supported studies. In the absence of motivation to do that for whatever reasons, we have felt compelled to move ahead to try to form a group to where we can answer these clinical questions, such as what's the most effective growth of methotrexate? Is there a ceiling effect or should you just continue to increase the dose? So we need to answer important clinical questions.

There are a variety of pediatric rheumatic

diseases that are even more rare than JRA, such as linear scleroderma or pediatric dramatamyocitis. We've been woefully inadequate in doing therapeutic trials on those groups and the market problem and the outcome measure problems are even more severe in those instances, and so we have made the decision to move ahead with trying to do studies in those populations that might not be of enough rigor or sophistication to allow the FDA to say, this is appropriate and strong enough data to do an indication, but it would be helpful to people who are still trying to take care of these patients.

So I think the major focus of that group will try to be to answer important clinical questions that aren't necessarily of market interest or of sufficient maturation to allow the FDA to kind of look at those kinds of studies.

But the potential exists also for this very large group to do pharmaceutical supported studies, so I think we could play it both ways, but we need to be realistic about what caused the organization of this international group.

DR. JOHNSON: I'm sorry, you really think what?

DR. LOVELL: We need to be realistic about what motivated and drove the organization of this group, which is actually, in some respects, a failure of the industry-supported, FDA-regulated approach to drug studies

in children.

DR. RIDER: By increasing your population and your population base, that you could eventually treat people as you may increase your industry support.

DR. LOVELL: That's true. That's true. I certainly wouldn't rule it out, and I'm not against it, because this is not a mechanism to allow us to study novel agents in JRA patients, really.

DR. JOHNSON: These are perceived as randomized studies, I take it, or--

DR. LOVELL: They could be done a number of different ways, but yes, they will be randomized studies. The first protocol we have is a randomized open study comparing various doses of methotrexate.

DR. JOHNSON: Let me make one comment. I hope we're not making the hurdle too high. I think anything that's clinically sort of defensible, we should approve a drug for if you show it works. There is a parallel in scleroderma. People are coming in with skin-sparing claims in scleroderma. Well, that's fair enough. That's an important dimension of the disease.

We tend to try to put caveats in there that at least the drug doesn't deteriorate the kidneys and the heart or X, Y, and Z, and it'll probably be some kind of the same

sort of orchestration with JRA. The subtype issue is a separate issue. The subset disease issue is separate.

Let me ask Bonnie one question. Imagine this scenario, that a company is working up a drug for adult RA and we have our sessions with the FDA and we say, try it in kids, and you convince your management to actually do a major study. Subset issue aside, you do a major study in JRA and the study doesn't quite make it. Now, is that the scenario--

DR. HEPBURN: I was going to ask you that question.

DR. JOHNSON: No. No. No. I think the spirit of where we're heading with labeling is that if it were a well-conducted study, we'd almost be obligated to put it into the label, even though it failed, and we couldn't give you a labeling, I suppose, because it did fail, but the information would be there and it may have failed for spurious reasons. I mean, in fact, your drug might work in kids. You just didn't show it in this case. But an individual clinician could come along and use it off-label, as we use methotrexate all the time.

DR. HEPBURN: That's not the issue that I was raising.

DR. JOHNSON: Okay, but would the possibility of

that scenario add impetus in your ability to convince management to go along with plans like this?

DR. HEPBURN: I think we've learned a lot, that since you've begun, not just in pediatric disease or rheumatic disease but in general to head toward descriptive labeling, that many of the trial results that never used to make it into the label will now be there--

DR. JOHNSON: Yes. I think they will.

DR. HEPBURN: --and that's very attractive to management.

DR. LOVELL: I think the new regulations, as described by you, are really a breath of fresh air, because I think it is important. I think that the hurdles have--I don't know if too high, too low is appropriate. I mean, you have to, as an FDA regulatory agency, feel like you're protecting--

DR. JOHNSON: Well, it's like Ed's comment before. I mean, if it really deteriorates the systemics, that's serious--

DR. LOVELL: Sure.

DR. JOHNSON: --and we wouldn't want to imply that we thought it worked due to some facile analysis.

DR. LOVELL: Right. But I think the reality is that the situation has not been productive for pediatric

rheumatology. If you do 25 trials and you get two NSAIDs approved, and that was a long time ago, I think that the way to look at it is there's a discordance between the level at which you have to raise your hurdles to feel like you're protecting the population and the level of hurdle that companies are willing to try to jump over at this current point in time, and we can't change the size of the market.

So I think there is this big discrepancy between the heights of the two hurdles, and my concern is that the current guidance material actually raised the height of the hurdle a little bit higher because it includes stuff that wasn't in there before, such as bone mineralization and functional things and quality of life and that sort of thing.

So my concern is that we've actually raised the hurdle, or will with these kinds of material, raise it even a little bit higher.

DR. JOHNSON: We never had old documents in pediatrics that were very established, and there was always this multiple measure problem. I think, if nothing else, if we get a core set of outcomes so that we can get a bipatient test--now, it's true the core set contains a functional measure, it doesn't contain a quality of life.

And I guess just by resolving some of the

ambiguities from the past makes the hurdle higher, in essence, because it's clear-cut. It was unclear where it was before, I guess, but I don't see any way around that, I mean, if you want to get an inference that has reliability to it.

Wouldn't you be uncomfortable as a clinician drawing a conclusion that a drug worked if the hurdle were as low as--if the hurdle were substantially lower? You wouldn't know if it really worked.

6:00 p.m. DR. LOVELL: Yes and no, but I think there's another way around it, and that is that we don't have to go for the full indication. I mean, the reality is, we're going to have to use the drugs anyway because we have to treat the patients, so we'll have to make the decisions about these drugs based on, I think, a much less satisfactory approach than trying to do formal studies that may or may not have all the bells and whistles in them. So I think we'll have to--I mean, these patients will be exposed to these drugs, for the most part.

But I guess the thing that really struck me when I read these guidances, we were trying to be--the wording was to try to make sure that the drug addressed all the issues that relate to a disease, and so, for example, to say a drug would not only improve the arthritis but would improve the

uveitis and the bone mineralization and nodules and things like that, we actually cast the net much broader than the old guidance.

DR. JOHNSON: We didn't actually say that, though.

DR. LOVELL: It wasn't clear to me when I read it how broad it was going to be stretched. Obviously, you didn't say you were going to require one drug to do all that stuff, but you did say that when you look at a drug, you ought to be looking at uveitis or fever or--

DR. JOHNSON: Yes. I don't think you can ignore that stuff because there would be the possibility that those things might get worse, and if you don't record them, then you'll never know.

DR. WALLACE: I'd like to make a comment, and Dan Magilavy touched on this and other speakers have touched on it, but I think we need to be very, very careful in the systemics in their active systemic phase not to confuse the macrophage activation syndrome that Ildy talked about and a drug reaction, and I think in the literature, those two have been confused and confounded and I think we need to be very careful when we're doing drug studies not to do that because we're going to overlook some very good drugs for systemics.

I think that if you look at those articles very carefully, all of those patients were in the active systemic

phase of their disease. It really appeared to me, in reading the majority of them, that they were probably in their macrophage activation system when they got the drug and it probably wasn't the drug. It just happened to be there when they continued to do their thing. So I just want to caution about that.

DR. JOHNSON: In a protocol, could you sort of stop and retest and so on, or would that be unethical? How would you literally design that in a protocol to differentiate? It's going to be very difficult.

DR. SILVERMAN: Can I address, though, that that's not a true statement? I will disagree. I've seen five patients and referred other patients who had no active systemic disease for years and two died of this syndrome. Others got fatal--not fatal, but very serious complications when their disease had been "no active systemic disease for years". Now, maybe I got wrong information. Maybe I can't read a thermometer, but I think so.

DR. CASSIDY: At the end of a very long day, I would like to make just a couple of comments, and I hope no one here will think that they are gratuitous.

As multiple speakers here have indicated, we face many challenges in pediatric rheumatology in designing better therapies for our children and we also face right now

many challenges as to whether we're going to be able to get the job done with the problems on the financial end and with the deterioration of the national stature of pediatric rheumatology.

I'm very encouraged by the very fact that this meeting was held for two reasons, which I'm sure you all have thought about. One, if we can encourage the FDA and industry to do more of these studies, then that gives our children a chance of having some therapies five years from now for their various diseases and it also gives us a chance to participate in the development of those therapies.

I would plead that we not focus totally on JRA, which we've done almost exclusively today. We have many other diseases, polyarteritis, the various other forms of vasculitis, dramatamyocitis. We have some diseases, I would allege, such as scleroderma, for which we have no therapy, and in the other diseases, we don't have a lot of good therapies, with perhaps the exception of Kawasaki disease.

So I am encouraged, Lisa and Kent, that we're having this meeting. I just hope that the ball now will really begin to quickly roll uphill.

DR. STRAND: I'm a little curious what we have done really to make some changes, to give outside organizations, be it industry or whatever, incentives to

study pediatric rheumatic diseases.

DR. LOVELL: What have we or what could we do?

DR. STRAND: Yes. What are we doing? What have we done? You are saying that you think that this and the regulation about pediatric labeling actually set the hurdles higher. Have we done anything to give them incentives, to give whomever incentives? Bonnie has a good point that maybe we can include adolescents with other rheumatic diseases in larger clinical trials, but to me, that still doesn't really get at the issue of pediatric rheumatic disease.

DR. HEPBURN: I think industry--you asked me if industry would be happy with some of this descriptive labeling. The next question is, how can they use this information, and that's going to be the question that's asked. If it's in the descriptive labeling and it's not a "indication", yet how can they say anything in the advertising?

DR. JOHNSON: Ask the Congressmen. I don't know.

DR. HEPBURN: But that's the next question. What does the industry get out of it?

DR. JOHNSON: But that still doesn't deter the clinicians from using it, obviously.

DR. HEPBURN: No, but it depends how the

information is disseminated.

DR. JOHNSON: Yes. I think the spirit is to make the labels substantially more descriptive for the successful and the unsuccessful trials, and it sounds to me like with the new rule, the final solution, the final rule, that sliding in a use for polyarticular JRA is going to be pretty straightforward, as long as you do a little PK work and some safety studies in kids, isn't that correct? I mean, that's--

DR. STRAND: But what's the difference between PK work and some safety studies in kids and a full-blown trial, because, in a sense, you can't do PK unless you've done single and multiple dosing, and you certainly can't do safety unless you've done adequate exposure.

DR. JOHNSON: Well, but it's--

DR. STRAND: I don't see how you get those two without the other.

DR. JOHNSON: Oh, sure. I mean, it's much less of a--

DR. STRAND: I'm not trying to be difficult. I'm just trying to say--

DR. JOHNSON: But it's much less of an outlay to do some PK work and even some open exposure than it is some formal clinical trials.

DR. HEPBURN: Usually, what we do with the PK, as you know, is go into one of the centers that's doing a multi-center trial and do your PK in that center, so it really isn't as difficult as doing it in a full-blown trial.

DR. MAGILAVY: And how many patient exposure years will be required in children?

DR. JOHNSON: You mean the open safety information? I have no idea.

DR. MAGILAVY: I think that's another--

DR. JOHNSON: It's important, yes, but it's surely not going to be equivalent to an NDA number. I doubt if there's any precedent at the agency so far to address the volume of information for either safety or PK.

MS. OLMSTEAD: We've gotten so few submissions at this point. We're working through this with each one and we've gotten probably just a handful. So, as you say, the issues regarding the indication and how can you market it if it's only in descriptive form, the issues about how much safety information is enough, we're going to be basically working through this step by step because it's not clear in the rule and it was kind of left to work through, because I think it's going to be different for each disease state that people come in with and the amount of information.

I think the intent of the rule is to try and

capture widely used drugs off-label, and I think in your particular disease state, because it's a much smaller population than some of the other ones that we're--the agency's actually looking to send some letters out to get their attention to say, the deadline's coming up. I think that's where it would have to go to the different divisions and work through with the clinicians and the divisions.

The divisions--actually, with this Pediatric Subcommittee, they're very committed to working with industry and academia to develop clinical trials at a much earlier stage and recognize that this labeling is not going to answer everything. That's strictly going to deal with what's out there already and may not even answer your questions, because you have such a small population and your population is so diverse that it sounds like only one subset of your population can actually use the rule because it's sufficiently similar to adults.

DR. JOHNSON: Yes. But the rule will apply to new drugs being worked up for adult RA, extrapolatable into--

MS. OLMSTEAD: Definitely. Definitely. But I would encourage--I put a plug in for anyone who's doing the clinical trials now that has direct contact with FDA to get in there and work with them directly because they're very committed to developing clinical trials for pediatrics as

early as possible. This is something that's really--they've been hitting on more and more.

DR. HEPBURN: It doesn't surprise me that people have not come in with applications for old drugs. There's not a whole lot there for them. I think you're going to see the effect more with the newer drugs coming along, where people can begin to think of the strategy as they're setting up their development plan and work into it. That's going to dribble in.

MS. OLMSTEAD: We're wrestling with the fact that some of these drugs are grandfathered and to change their labeling would require a new drug application, and who's going to submit a drug application for phenobarbital?

DR. HEPBURN: Right.

MS. OLMSTEAD: These are the things that we're wrestling with on this end, but I think you're right that the newer drugs will probably adhere to it sooner. The agency is trying to be as proactive at this point and start contacting sponsors to get a feel for, when do you expect to be submitting your supplements for planning purposes, to move away from the enforcement side of the rule and try to work through the letter of the intent of it, trying to get more information out there for the doctors and the pharmacists and the patients.

DR. STRAND: Because, I mean, there's experience whereby the PRCSG has had protocols for two biologic agents and studies ready to go and then the sponsors withdrew the availability of the agents. They weren't really even going to underwrite the studies or do much more than just supply product and maybe some monitoring.

DR. JOHNSON: Why did they back off?

DR. STRAND: Because they stopped development of both products in adult RA. Right now, with some experience with the large program internationally in adult RA, I still can't sell this sponsor on a pediatric indication. I cannot seem to get it across to them that there is financial incentive or really any incentive to do it. If we can't come up with the reasons that they should be interested in doing it, it's not going to happen.

DR. LOVELL: I think, from a pediatric rheumatology perspective, one thing that's been a big step forward in the last year or two is development of this core set and being very hard-nosed about outcome measures. One of the criticisms that we had on our own about our prior trials was we had a high placebo response rate, and I think a lot of it was due to the outcome measurement noise that we used. So we've been very hard-nosed about that and this core set, I think, represents a significant step forward.

The other thing that we've done that's been helpful to some extent is we've been able and willing to do these studies at a much less financial benefit than adult rheumatologists have, and the other thing we've done is we've written the grants to the FDA and got them funded, but that--

DR. STRAND: I think that's the big positive, is getting the grants funded. I think in terms of the incentives and costs, actually, real world nowadays, rheumatologists don't get a lot of reimbursement for doing clinical trials, either. The real world really, for now, is that the patient in the study actually gets their health care picked up in the study and that's the benefit and that ends up being the benefit for pediatric situations, as well.

But I'm just wondering, is there another way to make this more evident and at least it'll be in the discussion of today, which is important, because I think you're right about the core set. It's a minimum core set and you have to add other things, but it allows you to enroll basically all JRA patients with active disease once you have your criteria for enrollment and studying them with a single protocol, even if you have to add things to that, and that's very beneficial.

DR. JOHNSON: Yes. I would second that.

Has anybody had any experience with an attempt to do collaborative industry-HMO studies? Kaiser, I have understood, was predisposed to be interested in this, I read somewhere.

DR. STRAND: Only in certain indications.

DR. JOHNSON: Talk about captive populations, you know.

DR. STRAND: Only in certain indications, and so far--

DR. JOHNSON: JRA is not on the list, huh?

DR. STRAND: In adult rheumatology--

DR. MAGILAVY: Asthma, maybe.

DR. JOHNSON: Well, it's something to keep in mind as managed care sweeps over the country.

CLOSING REMARKS

DR. RIDER: Are there any final comments before we close today?

We'd like to very much thank everyone for their participation today and we very much appreciated your thoughtful input into the discussions that we've had and into your presentations. We'll very carefully consider this in revising the draft guidance document.

In addition, the docket will remain open for comment until August 30 and all comments will be carefully

considered by the Rheumatology Working Group.

I'd finally like to thank Dr. Janet Woodcock for her vision in organizing the Rheumatology Working Group, providing support for the rheumatoid arthritis guidance document, and also providing support for the funding that enabled this meeting today.

I'd also like to thank my co-organizer, Kent Johnson, for all his vision in organizing this meeting, as well as Rose Cunningham and her staff for organizing all of the details of our day.

At this time, we would like to invite you to participate in a dinner tonight. All participants and audience may participate in a dinner at the Cottonwood Cafe on Cordell Avenue.

Thank you.

[Whereupon, at 6:14 p.m., the meeting was adjourned.]

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